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X-ray diagnosis
Nuclear medicine
Ultrasound
Nuclear magnetic resonance
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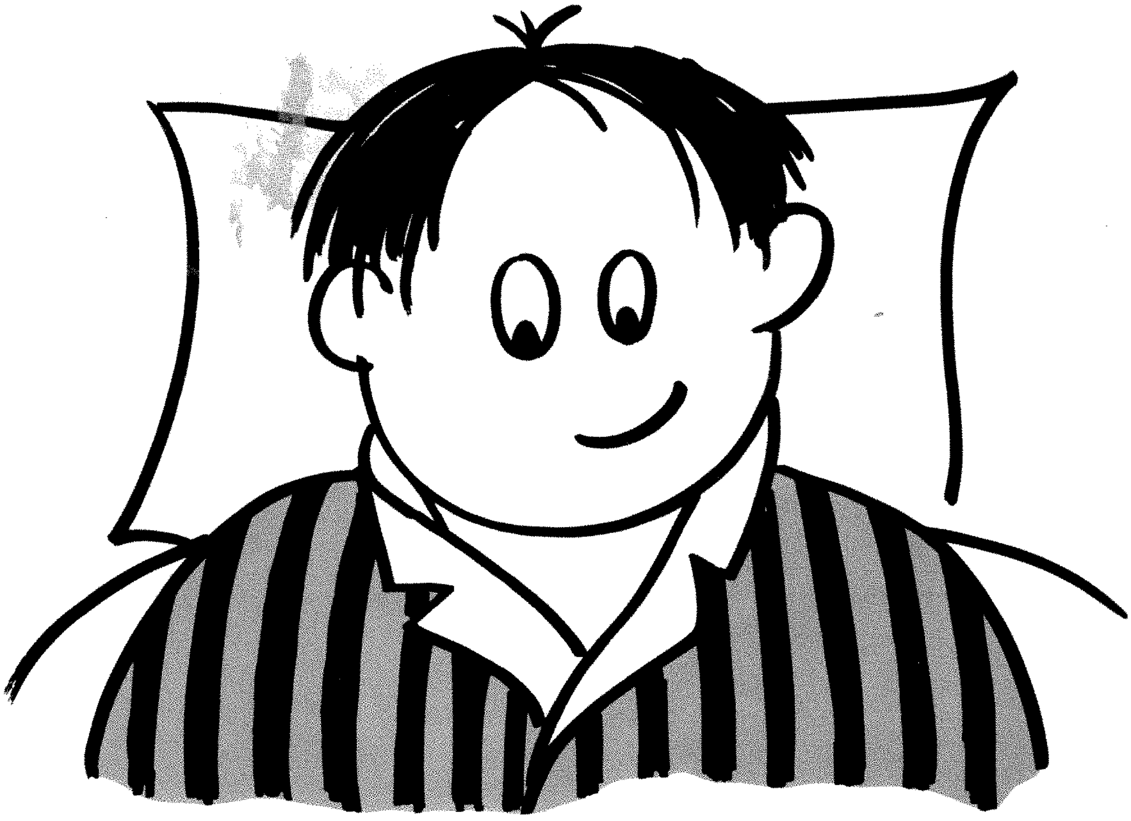

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References: 1. Julien RM. Effects of nalbuphine on normal and oxymorphone – depressed ventilatory responses to carbon dioxide challenge. Anaesthesiology 1982; 57: No 3A. 2. Fahmy NR, Sunder N, Soter NA. A comparison of histamine releasing properties and hemodynamic effects of morphine and nalbuphine in humans. Anesth Analg 1984;63:175. 3. Vatashsky E, Haskel Y. The effect of nalbuphine (Nubain®) compared to morphine and fentanyl on common bile duct pressure. Curr Ther Res 1985;37,1:95-102. 4. Shah M, Rosen M, Vickers MD. Effect of premedication and diazepam, morphine or nalbuphine on gastrointestinal motility after surgery. Br J. Anaesth. 1984;56: 1235-8.
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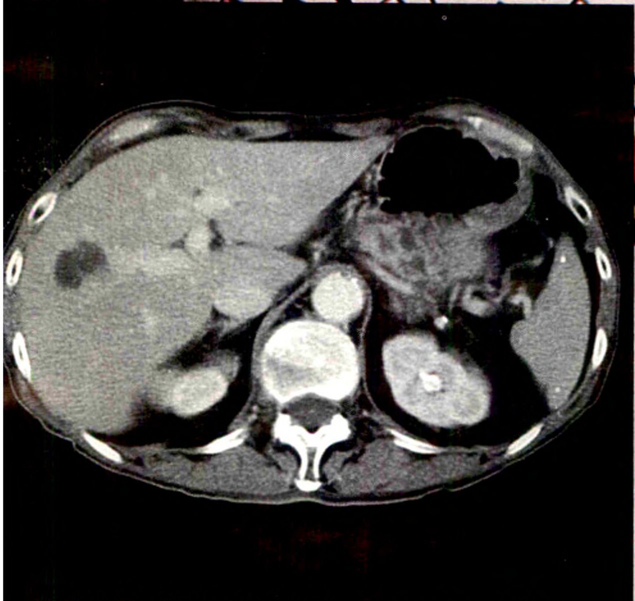
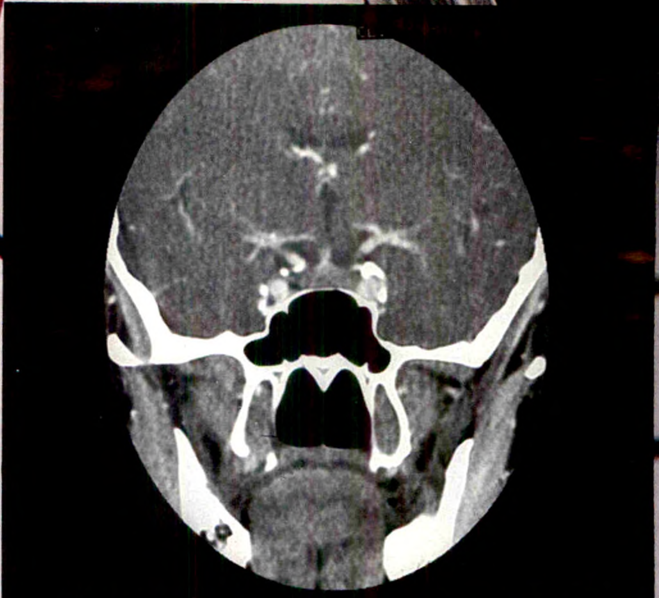
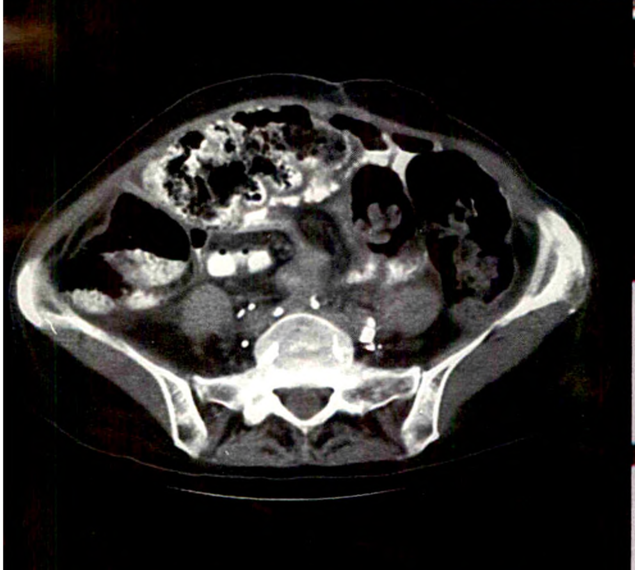


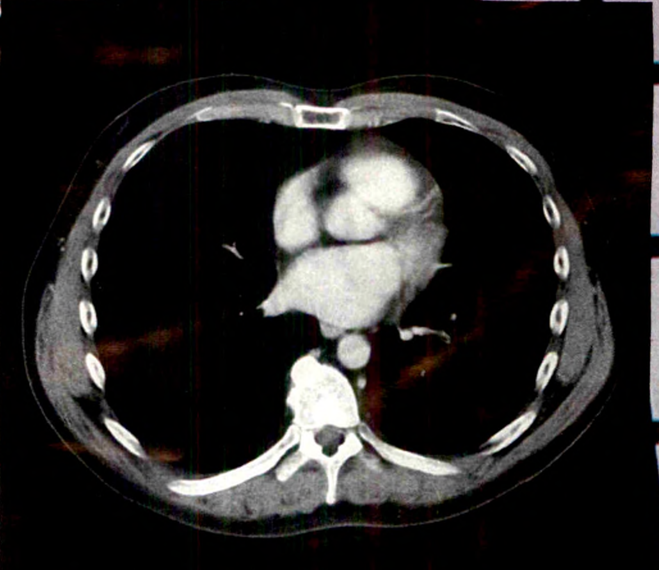
Visualization of liver metastases. No motion artifacts from gastric air level.



Dynamic scan shows normal upward bulge of pituitary at the insertion of the infundibulum.



Bowel wall and vessels clearly demonstrated. Minimal streaking from air/contrast levels.



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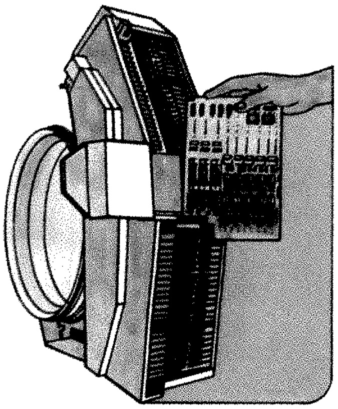

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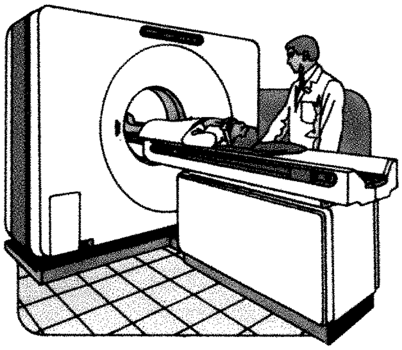

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Mayneord Lecture 1987

The Mayneord Lecture is financed through the generosity of 3M United Kingdom PLC. It is named after Professor W. V. Mayneord CBE, FRS, Past President and Honorary Member of the British Institute of Radiology. The Award is made annually to an individual or to a group of collaborators in recognition of recent or current major contributions to the wide and expanding field of radiology.

Nominations for the fourth lectureship to be delivered at Radiology '87 are invited and should include a curriculum vitae and a clear, concise statement of the work on which the lecture is to be based, which must come within the wide field of interest of the British Institute of Radiology. The recipient will be selected by a committee comprising the President and senior Vice President of the British Institute of Radiology and a senior member of 3M United Kingdom PLC. Please send nominations to the President, The British Institute of Radiology, 36 Portland Place, London W1N 3DG before *1st May 1986.*

The third Mayneord Lecture entitled **Seeing things more clearly** will be given by Mr G. R. Higson BSc, FInstP, CEng, FIEE, Director, Scientific and Technical Services, Department of Health and Social Security. It will be given at the Unicorn Hotel, Bristol, on Wednesday 9th April 1986 at 5.00 pm during the BIR Annual Congress RADIOLOGY '86.

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Kodak Limited, together with the Royal College of Radiologists, has established The Kodak Trust for Radiology.

The purpose of the Trust is to provide funds in support of suitable projects of benefit to and for the promotion of radiology, which is defined in the Trust Deed as "the science of the use of radiations (both ionising and non-ionising) and associated techniques in the investigation, diagnosis and treatment of disease."

The Trust now invites applications for research grants. The closing date for the receipt of completed forms and details is **31 March 1986**

Application forms and further details may be obtained from:

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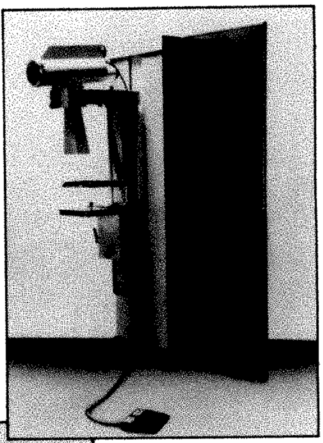

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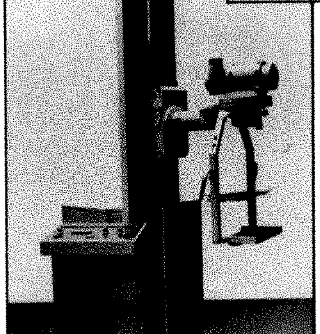

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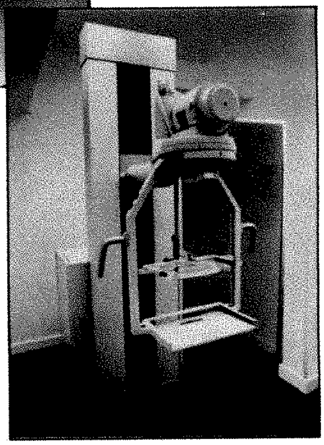

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ULTRASOUND AND IMAGING IN BESANÇON
(France)
APRIL 2–3–4, 1986

APRIL 2

8.40	Welcome address	**Prof F Weill**
8.55	Sonoanatomical introduction: Abdominal vessels	**Prof F Weill**
9.15	Ultrasonic study of arterial aneurysms and dissection; comparison with CT and MRI	**Dr D Didier**
9.45	Sonoanatomy of the kidney and retroperitoneum	**Prof F Weill**
10.10	Break–Visit to technical exhibition	
10.30	Renal ultrasound in 1986	**Prof F Weill**
11.30	Ultrasound in the follow-up of renal transplantation	**Prof M Manco Johnson (Denver–USA)**
14.30	CT of the urinary tract and adrenals	**Prof A Baert (Leuwen–Belgium)**
15.30	Break–Visit to technical exhibition	
16.00	Ultrasound of the lower urinary tract	**Prof H Holm (Copenhagen–Denmark)**
17.00	Ultrasonic study of abdominal lymphnodes	**Prof F. Weill**
17.30	End of the session–Visit to technical exhibition	
18.30	Informal get-together reception in "Palais Granvelle"–Grande Rue.	

APRIL 3

8.15	Artifacts in ultrasonic imaging	**Prof F Winsberg (New York–USA)**
9.15	Liver ultrasound in 1986	**Prof F Weill**
10.15	Break–Visit to technical exhibition	
10.45	CT of the liver	**Prof J L Pistolesi (Verona–Italy)**
11.45	Ultrasound of the spleen	**Prof F Weill–Dr Coche**
14.00	Visit to technical exhibition	
14.30	Ultrasonic study of pancreatic disease, with reference to CT	
	–Pancreatic tumours	**Prof F Weill**
	–Acute pancreatitis	**Prof F Weill and Dr P Rohmer**
	–Chronic pancreatitis	**Dr D Didier**
15.45	Break–Visit to technical exhibition	
16.15	Ultrasound of the digestive tract	**Prof L Oliva (Genoa–Italy)**
17.00	Biliary ultrasound in 1985	**Prof F Weill–Dr Coche**
17.45	Pre-endoscopic ultrasound	**Prof H Lutz (Bayreuth–Fed Rep of Germany)**

APRIL 4

8.15	Ultrasonic and CT study of the peritoneum: A guide to the interpretation of the acute abdomen	**Prof F Weill and Dr J Watrin**
9.00	Sonopediatrics 1: Digestive pathology	**Prof V Tran-Minh (Lyon–France)**
9.50	Sonopediatrics 2: The urinary tract and retroperitoneum	**Prof V Tran-Minh**
10.30	Break–Visit to technical exhibition	
10.50	Neonatal neurosonology	**Prof M Manco-Johnson (Denver–USA)**
11.30	Foetal interventional sonology	**Prof M Manco-Johnson**
14.00	Guided biopsy and interventional sonology	**Prof P Bret (Montreal–Canada)**
15.00	Per-operative ultrasound	**Prof M C Plainfosse (Paris–France)**
16.00	What's happening in the neighbour's yard: –Magnetic resonance imaging of the abdomen	**Prof W Curati (London–England)**
16.45	–Magnetic resonance imaging of the thorax	**Dr D Didier**
17.00	End of the seminar	

Registration details from:
Prof F Weill, Radiologie A, Hôpital J Minjoz,
Blvd Fleming, 25000 Besançon, France.
Registration fee: US$135.00 FF1.100
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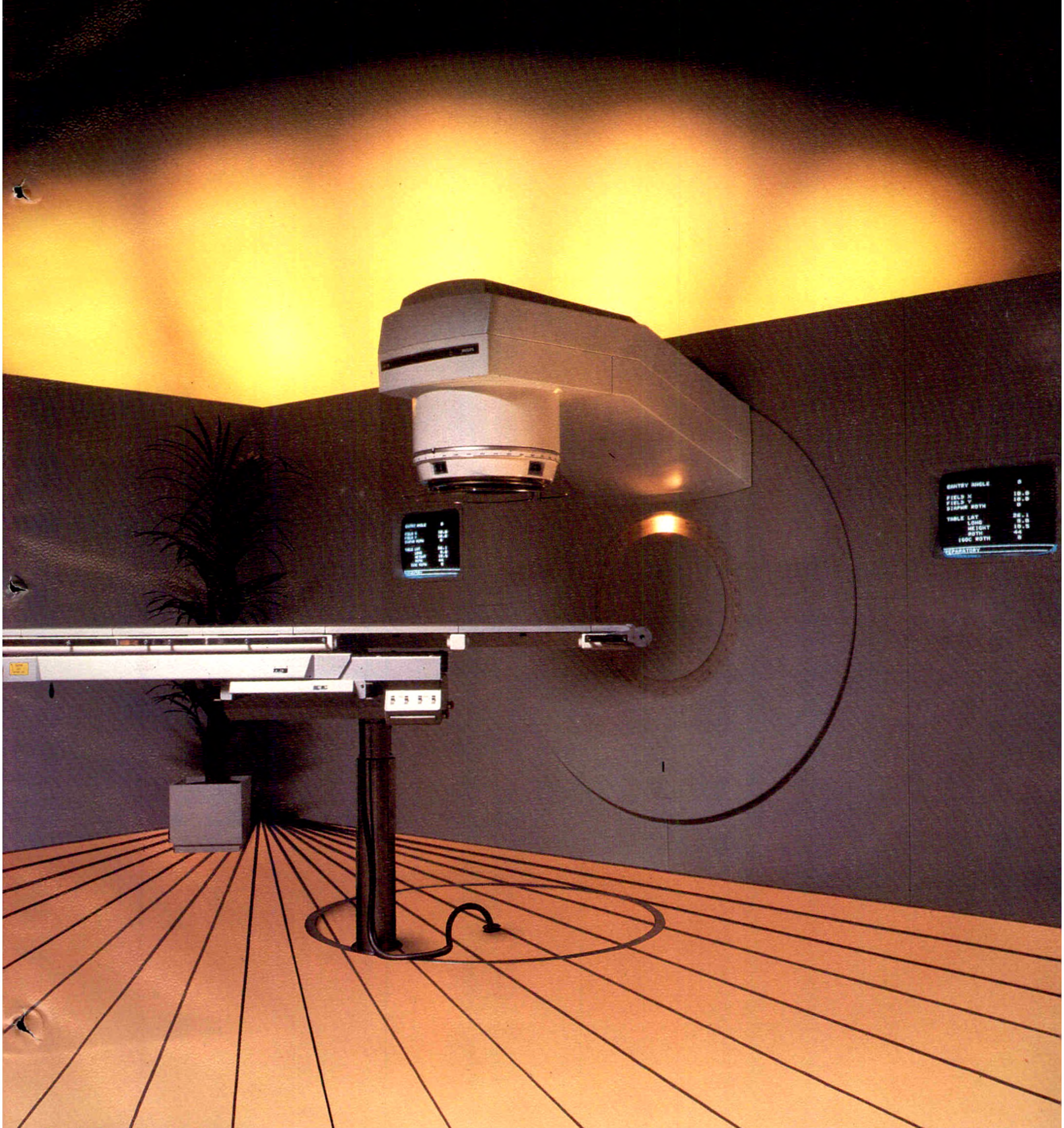

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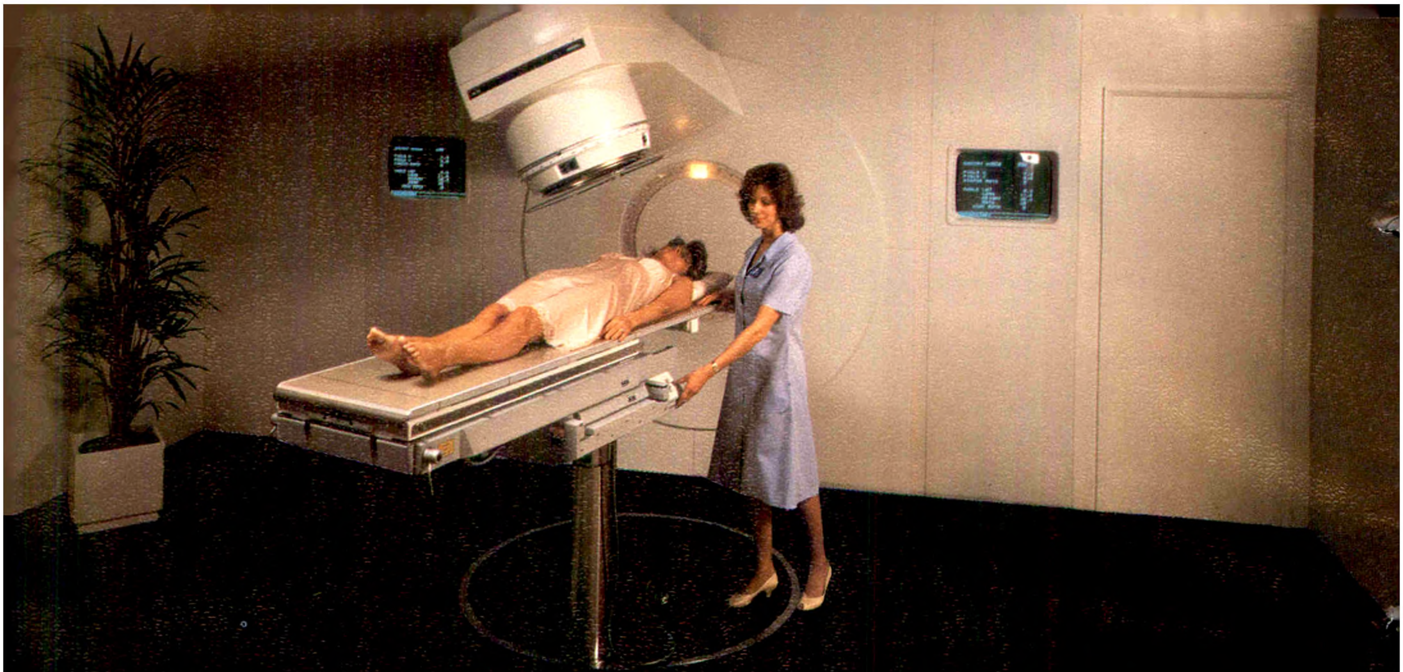

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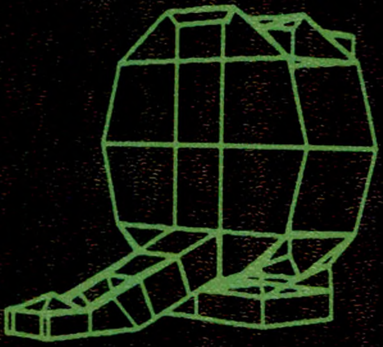

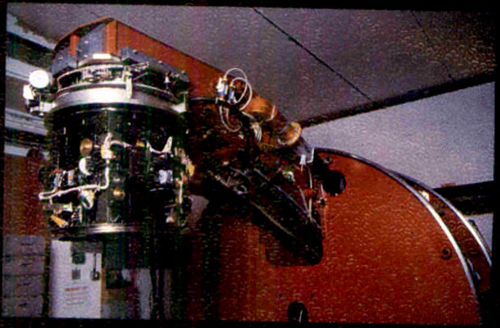

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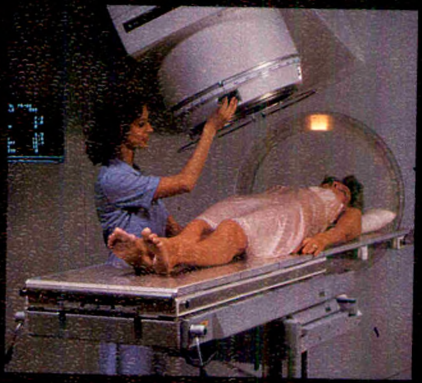

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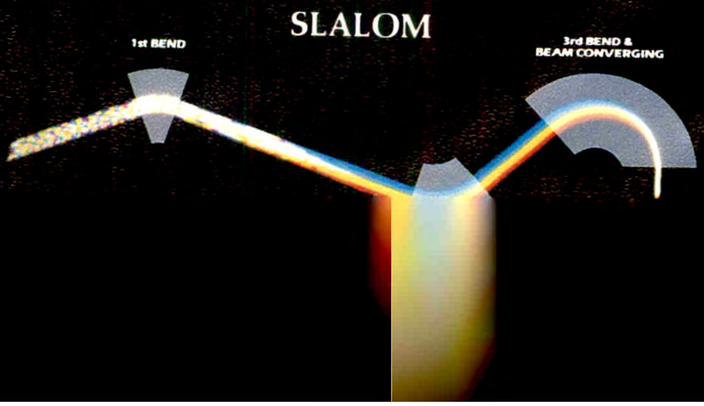

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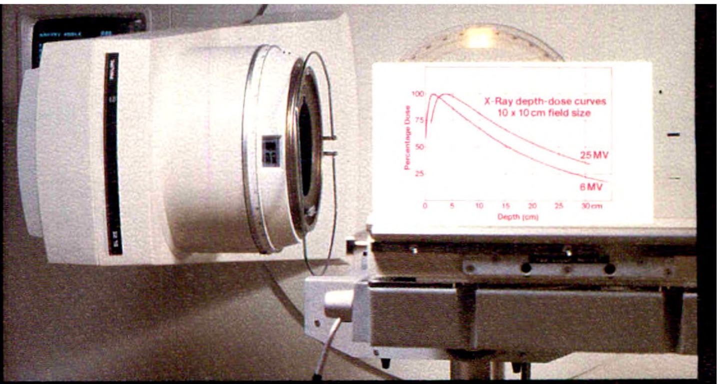

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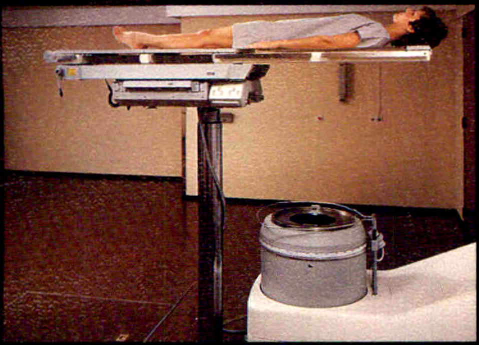

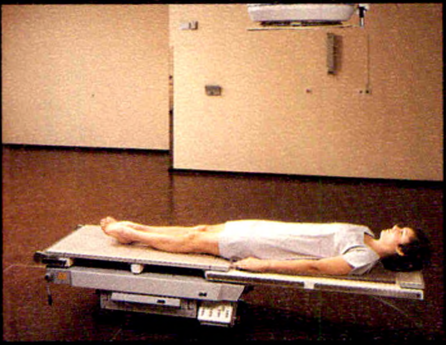

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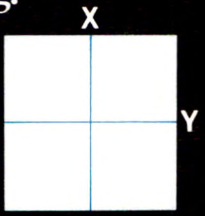

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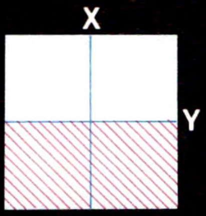

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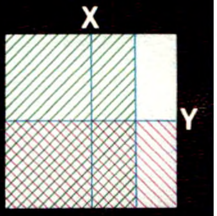

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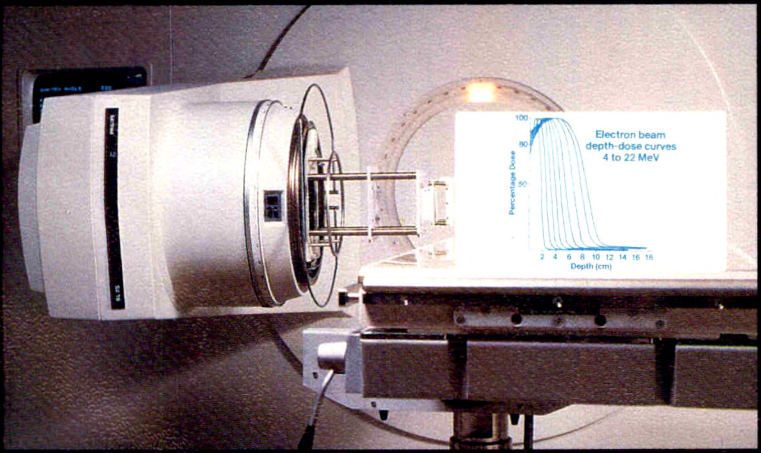

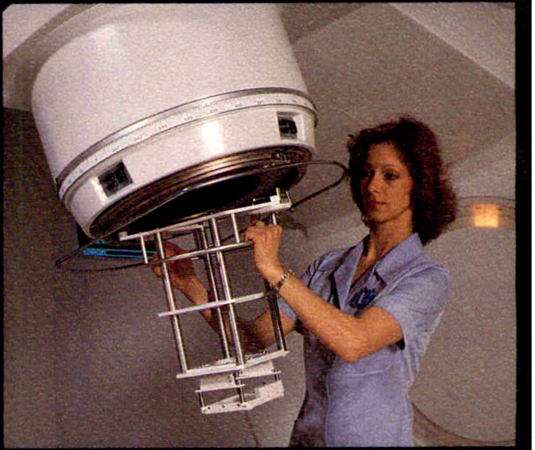

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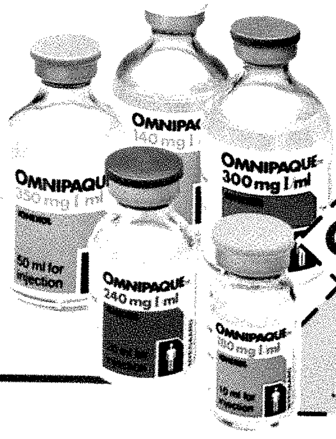

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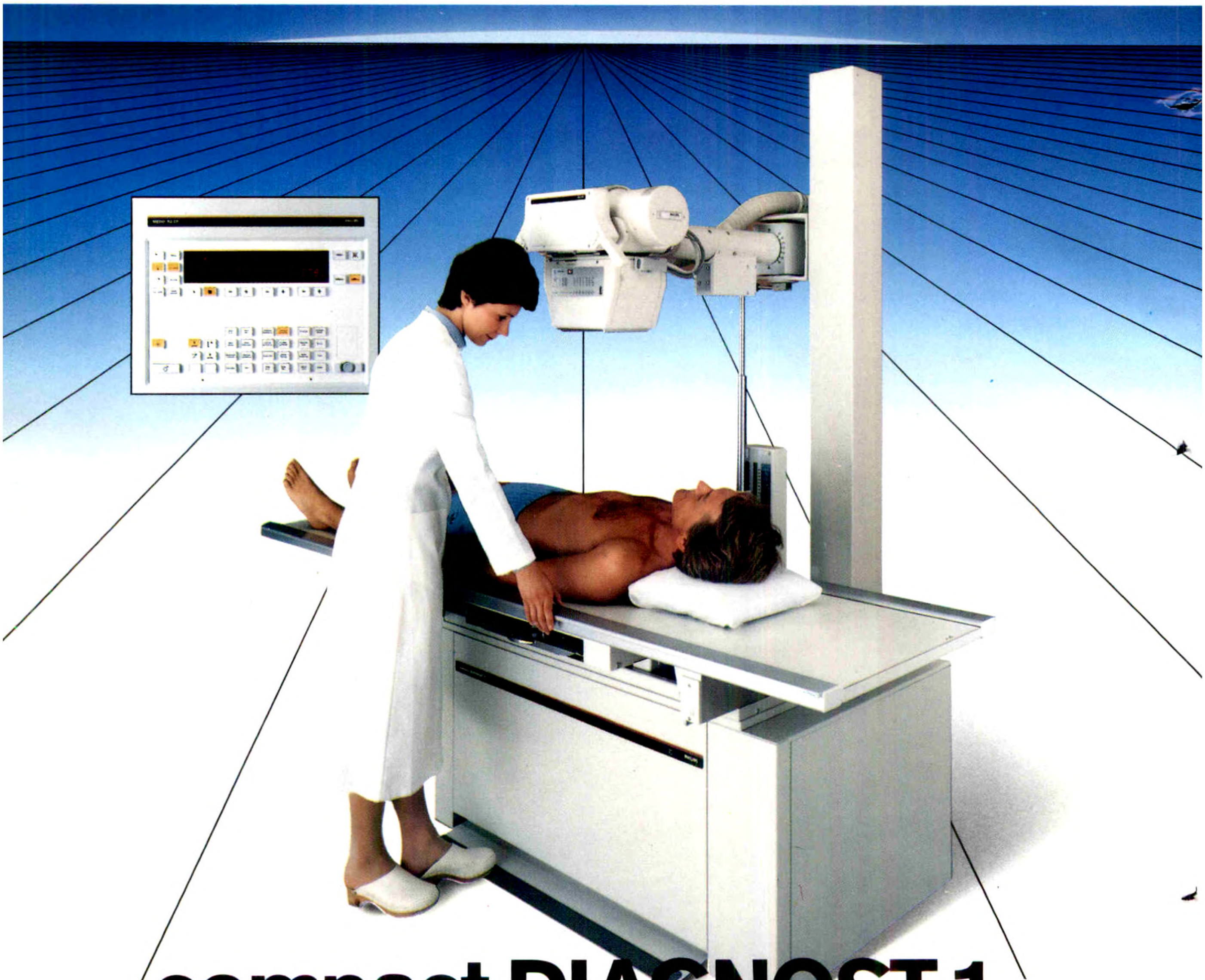Integrated systems technology

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VOLUME 59 NUMBER 697 JANUARY 1986

The British Journal of Radiology

Editorial

Diagnostic radiological examinations of women of reproductive capacity

It is of the nature of radiation safety recommendations that they are almost always based on statistically imprecise data; that they often involve the estimation of low-dose response from relatively high-dose information, and that they may depend on the radiological interpretation of non-human evidence. It is appropriate, therefore, to review the available evidence from time to time and to update practical procedures, as necessary, to take account of new knowledge.

Arising from their continual and authoritative review, the International Commission on Radiological Protection have issued a Statement (ICRP, 1984) on the diagnostic exposure of women, supplementing their more comprehensive recommendations on the protection of the patient in diagnostic radiology (ICRP, 1982). Current advice is aimed at confining less urgent radiological examinations to the 10 days following the start of menstruation. However, the ICRP Statement indicates that this advice can now be modified. An article presenting the relevant clinical and radiobiological considerations appears in this issue (Russell, 1986). The key paragraph of the ICRP Statement reads:

> "During the first ten days following the onset of a menstrual period, there can be no risk to any conceptus, since no conception will have occurred. The risk to a child who had previously been irradiated *in utero* during the remainder of a four-week period following the onset of menstruation is likely to be so small that there need be no special limitation on exposures required within these four weeks."

In March 1985 the National Radiological Protection Board issued its own concordant advice entitled, "Exposure to ionising radiation of pregnant women: Advice on the diagnostic exposure of women who are, or who may be, pregnant" (NRPB, 1985). This advice supersedes the 10-day rule.

Both documents point out that risks of inducing malignancy or developmental malformations may result from irradiation at later stages of pregnancy (UNSCEAR, 1972; Otake & Schull, 1984). Such risks which, depending on radiation dosage, will usually be less than the concomitant risks associated with any pregnancy, have to be off-set against the benefit to the patient from the radiodiagnostic procedure.

In considering the appropriate practical response to these recommendations, it is appreciated that local conditions vary to such an extent that any centrally promulgated rules to replace the 10-day rule might prove difficult to implement. The Royal College of Radiologists has, however, indicated advice which it feels may be of value to radiologists in the implementation of new procedures (Roebuck, 1985). The BJR was grateful for the opportunity of a preview of this practical advice, to which it gives its support and of which the essential features are given below.

If a woman is pregnant, or considers that she may be pregnant, then direct irradiation of the abdomen and pelvis should, whenever possible, be avoided, especially during the third and fourth months after the onset of the preceding menstruation. Other examinations may proceed provided there is good beam collimation and protective shielding of the abdomen and pelvis.

The referring clinician should ascertain if the patient is pregnant and, if so, should state if there are overriding clinical reasons for the requested examination to proceed. This may require some modification of existing request cards. In cases of pregnancy or suspected pregnancy, the radiologist and/or the referring clinician should decide whether the requested examination should proceed, be modified, or be postponed.

Departmental staff should enquire of women of child-bearing age referred for examinations involving direct irradiation of the abdomen or pelvis, if they are, or may be, pregnant. If this duty is devolved to clerical staff, it may be prudent to issue a list of those examinations which entail direct irradiation of the abdomen and pelvis (*e.g.* lumbar spine, urography, etc.).

It is further suggested that notices be placed within the X-ray department, requesting that patients who are, or think they might be, pregnant inform the radiographer or the radiologist before the examination is carried out. A woman who is not certain that she is not pregnant should be treated as though she were pregnant.

The 10-day rule has also been applied to Nuclear Medicine investigations, with the reference to abdominal/pelvic irradiation being interpreted as a dose of radiopharmaceutical which gives a gonad dose in excess of 50 mrad (0.5 mSv) (Ellis et al, 1977), although this criterion has not been universally accepted. Departments which currently apply the 10-day rule to the booking of Nuclear Medicine investigations should therefore modify their procedure to that of an enquiry of suspected pregnancy, as indicated above.

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1986, *The British Journal of Radiology, 59*, 3–6 JANUARY 1986

The rise and fall of the ten-day rule

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(Received June 1985 and in revised form August 1985)

ABSTRACT

The introduction of the 10-day rule is described together with the difficulties arising from its application. The reasons for believing it is now unnecessary are summarised. The new recommendations from the National Radiological Protection Board stress the importance of identifying a pregnancy after a period has been missed and provide advice regarding the radiography of the patients. The rationale of these suggestions is given. The importance is stressed of keeping both male and female gonad doses to a minimum during the reproductive years.

The fetus is sensitive to radiation. It is, therefore, superficially attractive to avoid irradiation of a pregnancy whenever possible. The International Commission on Radiological Protection (ICRP, 1970) recommended that "All radiological examinations of the lower abdomen and pelvis of women of reproductive capacity, that are not of importance in connection with the immediate illness of the patient, be limited in time to the period when pregnancy is improbable (the ten day interval following the onset of menstruation). The examinations that it will be appropriate to delay until the onset of the next menstruation are the few that could, without detriment, be postponed until the conclusion of a pregnancy, or at least its latter half" (see also ICRP, 1964). A similar recommendation was incorporated into the United Kingdom Code of Practice (Department of Health and Social Security (DHSS), 1972).

The original proposal (in terms of 14 days rather than 10 days) was suggested by Russell and Russell (1952), based on their work on radiation damage to organogenesis of mouse embryos. The reduction to 10 days arose out of variability of the human menstrual cycle, and hence of the time of ovulation. The Royal College of Radiologists (1975) published a note on how the 10-day rule could be implemented (this was said to be the first time in over 400 years that any Royal College had made a recommendation on a clinical matter).

The Royal College paper indicated that only examinations which involved the uterus in the primary beam need be considered and if a woman could positively affirm that she was not pregnant, because she had had no recent sexual intercourse, or had had satisfactory contraception or who had had a surgical sterilising procedure, then they need not be scheduled to the first 10 days. The referring clinician was to be asked to indicate whether the examination was urgent enough to ignore the 10-day rule. This meant that a hospital with 100 000 radiological examinations a year would have only to schedule about two patients a week (Table I), and it was felt that this additional workload would not be too difficult to manage.

However, problems arose. Sometimes clinicians refused to co-operate. There are patients who do not speak English and discussion of a patient's menstrual cycles in the middle of a busy department is embarrassing for everybody. Many patients have irregular menstrual cycles and, at times, when a patient returns for an examination which has been scheduled it is found that her period is delayed for one reason or another and further visits to the department are necessary. Difficulties arise with radioisotope examinations (Ellis et al, 1977).

Other countries found that the 10-day rule did not significantly disturb their practice. In some (National Council on Radiation Protection and Measurements (NCRP), 1971) it was argued that the rule was too restrictive. In many countries an examination is nearly always carried out within a day or two of its being requested. Thus, the referring clinician determines the timing of the examination, with his knowledge of the urgency of the case. In Britain, delays of days or even weeks are more common, so the radiologist has to take responsibility for the timing.

ARGUMENTS AGAINST THE TEN-DAY RULE

These fall under four headings, as follows.

Timing

Russell and Russell (1952) recommended scheduling to avoid damage to organogenesis by radiation. But with humans, organogenesis does not start until the third week after conception (Goulden & Murry, 1980). Thus, failing to schedule within the menstrual cycle does not allow a possible radiation injury to organogenesis.

Radiobiology

There is no evidence to allow one to be certain that irradiation of a conceptus in the early weeks of pregnancy is more or less dangerous than irradiation of the ovum in the weeks before fertilisation. Human data are sparse, and we have often to extrapolate from animal studies.

In the human ovum the first reduction division (meiosis) begins in the fetus, but is arrested in the

TABLE I

FREQUENCY OF SCHEDULING IN A HOSPITAL WITH 100 000 ATTENDANCES FOR RADIOGRAPHIC EXAMINATIONS

Total patients	100 000
Female	50 000*
Of childbearing age (Kendall et al, 1980)	18 500
Of whom 95% can say they are not pregnant (McCreath et al, 1975)	925
Half are urgent enough to ignore 10-day rule	470
One fifth of examinations include the uterus in the primary beam (Kendall et al, 1980) giving number to schedule	100

*Figures are rounded

diplotene phase after DNA replication has occurred. The oocyte stays in this arrested state until some weeks before ovulation when the first meiotic division is completed. The second reduction division then starts and is completed after fertilisation. During the long resting diplotene phase, it is suggested by animal experiments, with confirmation by human observations, that the oocytes are resistant to induced mutations and translocations (Baker & Neal, 1977). In contrast, the oocytes in multilayered and Graafian follicles are more sensitive to genetic injury, particularly between metaphase I and metaphase II, *i.e.* the ending of meiosis I and into meiosis II. This period occurs during the 6 or 7 weeks before ovulation, at which time the mutation rate from irradiation increases sharply (Committee on the Biological Effects of Ionizing Radiations (BEIR), 1980). The beginning of this sensitive period coincides with the formation of the zona pellucida and a change in the nuclear morphology of the oocyte. In the radio-resistant dictyate phase the chromosomes are surrounded by a thick sheath of ribonucleoprotein granules, which is greatly thinned in the more sensitive phases (Baker & Neal, 1977). High dose-rate exposures, which occur in primary beam radiography, are more mutagenic than a similar radiation dose at a slow dose-rate (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 1982).

How big is the risk of genetic injury? The risk assessed by UNSCEAR (1982) is a doubling of the spontaneous mutation rate for a 1 Gy exposure. This gives 0.00012 cases/cGy of serious genetic ill health (Oftedal & Searle, 1980) in the first two generations. However, this figure is for a low dose-rate exposure throughout life. It must be multiplied by a factor of around 20 (BEIR, 1980) for the exposure in the 6–7 weeks prior to conception and by a further factor for the high dose-rate associated with diagnostic radiography (BEIR, 1980). This risk can be compared to the hazard of radiation exposure in pregnancy. The risk of cancer and organogenesis derangement is in the range of 0 to 0.001 cases/cGy (Mole, 1979). It can be seen that the risk of a serious radiation injury is comparable and could be greater in the 7 weeks before the mother becomes pregnant than in the first 2 weeks of pregnancy.

Magnitude of the hazard

The risk seems to be insignificant. It has been shown (Russell, 1984) that, taking the hazard at the worst, we could expect one extra case of abnormality in 30 years in the United Kingdom. The delay in diagnosis in the scheduled patients could entail hazards to both mother and fetus to outweigh a benefit from the 10-day rule.

Cost-effectiveness

The cost of implementing the 10-day rule appears to be some 100 times greater than the value of the possible benefit derived from it (Russell, 1985), assuming a benefit exists.

PRESENT ADVICE

The ICRP (1984) have now withdrawn support for the 10-day rule. They say "During the first ten days following the onset of a menstrual period, there can be no risk to any conceptus, since no conception will have occurred. The risk to a child who had previously been irradiated *in utero* during the remainder of a four week period following the onset of menstruation is likely to be so small that there need be no special limitation on exposure required within these four weeks".

The National Radiological Protection Board (NRPB, 1985) in following this lead, add the following advice

> "*Diagnostic examination of women of reproductive capacity*
>
> It would be prudent for referring physicians and radiologists to treat as pregnant any woman being considered for, or presenting for, radiography at a time when a period is known to be overdue or clearly missed, unless there is information indicating the absence of pregnancy. If the cycle is so irregular that it is difficult to know whether a period has been missed, then a pregnancy test may help to determine whether the patient is pregnant.
>
> In order to minimise the frequency of unintentional exposure of fetuses it is recommended that, other than in dentistry, arrangements should be made for any woman for whom irradiation for diagnostic or therapeutic purposes is being considered, and where the uterus may lie in or near the useful beam, to be invited to answer the question, "Are you, or might you be, pregnant?". Unless the answer is "No", the woman should be regarded as if she were pregnant. The arrangements for posing the question may vary. Suggestions range from a prominent notice, through the use of a printed card handed to the selected patient, to an oral question.
>
> When a pregnant woman requires a radiographic examination in which the primary beam irradiates the

fetus, special care should be taken to ascertain that the examination is indeed indicated. The risk as a result of irradiating the fetus may be much less than that of making a necessary diagnosis, so that the examination should still be made if properly indicated. In such a case, greater than usual care should be taken to minimise the number of views and to minimise the absorbed dose per view. However, these precautions should not be taken to the detriment of technique and the diagnostic value of the examination.

When radiography of areas remote from the fetus is required, such as the chest, skull, or hand, this may be done safely at any time during the pregnancy with good collimation and properly shielded equipment. The dose to the uterus of a woman from a chest X-ray is usually less than 10 μGy Further information is available in a report from the International Commission on Radiological Protection (1982).

This advice supersedes the earlier recommendations from both national and international bodies aimed at confining the less urgent radiological examinations to the ten days following the start of menstruation—the so-called ten-day rule."

RESULTS OF THE NRPB ADVICE

Pregnancy is here defined as beginning after a period is overdue, so there need be no special limitation on exposures during a cycle—the 10-day rule is dead.

However, NRPB are anxious to establish a protocol to identify women who are more than 2 weeks pregnant, *i.e.* when organogenesis has commenced: in the human, organogenesis begins in the third week after conception. Recent work (Otake & Schull, 1984) has shown that identifiable injury to brain growth can occur, assuming a linear dose-effect function, at a rate of 0.005/cGy. There are, of course, many other organs developing besides the brain. The period of organogenesis extends up to the end of the first half of pregnancy. Obviously diagnostic exposure during this time should be avoided if possible or kept to a minimum compatible with proper medical care

With this official advice to identify early pregnancy there is both a medico-legal and a radiological reason for being certain that pregnancies of more than 2 weeks are not inadvertently irradiated. Many radiologists will be unhappy to rely on a printed notice for this. Many women cannot read English and notices may not be seen or may not be read because glasses are not worn. Memories of patients and staff are fallible and most departments will probably rely on a question on the request form to be initialled by the radiographer when examining females of child bearing age. This could read

Pregnant? Yes/No
Radiographers signature...... ... .

If a woman might be more than 2 weeks pregnant (*i.e.* she has missed a period) and if the uterus lies in or near the primary beam, then the radiographer should consult with the referring clinician or radiologist unless the clinical situation (*e.g.* a fractured pelvis) dictates otherwise. If the examination is to proceed, special care should be taken to minimise the absorbed dose per view.

In the non-pregnant woman the ovum is particularly sensitive to radiation from 7 weeks prior to ovulation. The testis is similarly sensitive during spermatogenesis, which may be up to 6 months prior to ejaculation. The testis is about five times more sensitive to radiation mutagenic injury than the resting ovary (BEIR, 1980). It would restrict medical care considerably to avoid irradiation during these periods, so the need to keep radiological exposure of the gonad to a minimum until reproduction is finished cannot be over-stressed. Careful collimation of the beam and the use of gonad shields will substantially reduce the gonad dose (Wall et al, 1980). With no 10-day rule, good practice often will also reduce the dose to a very early pregnancy, *i.e.* before a period is missed.

RADIOLOGICAL GROUNDS FOR ABORTION

With no 10-day rule, embryos within 2 weeks of fertilisation will occasionally be subject to inadvertent medical irradiation, and this may also occur at other times during pregnancy. There was general agreement from many national authorities (British Institute of Radiology (BIR), 1974) that after an exposure of less than 10 cGy a pregnancy should be allowed to continue. The work of Otake and Schull (1984) will lead many to reduce this upper limit to 5 cGy in the second quarter of pregnancy. The mean gonad dose for nearly all examinations surveyed by Wall et al (1980) was less than 1 cGy, except for barium enemas in women where the mean dose was less than 2 cGy. In early pregnancy the dose to the uterus may be assumed to be the same as that to the ovary. Where there has been inadvertent exposure of a pregnancy, an estimate of dose should be made. The gonad dose for similar examinations can vary by two orders of magnitude or even more between different hospitals (Wall et al, 1980). This observation underlines again the need for careful radiography.

Of recognised pregnancies, 15% end in abortion and 1% of the newborn have a serious abnormality (UNSCEAR, 1982). Taking a 0–0.1% cGy hazard of tumour or a serious maldevelopment (Mole, 1979), it can be seen that the radiogenic risk, although unwelcome, is bearable. Radiology is only one of the hazards of pregnancy. Nora et al (1967) found that women were exposed, on average, to 3.7 different potentially teratogenic agents in the first 3 months of pregnancy.

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Parametric imaging using digital subtraction angiography

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ABSTRACT

Digital subtraction angiography following an injection of iodinated contrast material can regularly produce good quality images In addition to the conventional anatomical information, the timed sequence of digital images also contains useful temporal information which hitherto has been largely ignored. A simple method of image processing is described which utilises this timing information and presents it as a colour-coded set of functional images Three parameters MAX, T-MAX and T-½ MAX are extracted from time–density curves, analogous to the time–activity curves of Nuclear Medicine, on a pixel-by-pixel basis. These parameters are used as a measure of overall organ perfusion, blood transit time between different vascular compartments, and as an indication of the initial delivery of contrast material to an organ. They have found use in the analysis of myocardial perfusion, before and after pharmacological intervention, and in the examination of the cerebral and renal circulations. The potential advantages of this technique derive from its superior spatial, temporal and contrast resolution

Digital subtraction angiography (DSA), with its enchanced contrast resolution, was developed with a view to performing angiography following a peripheral venous injection of iodinated contrast material. Intravenous DSA is able to provide good anatomical detail, and has found use in both peripheral and central vascular studies. The theory of operation of DSA has been described in several publications (Brody et al, 1982; Harrington et al, 1982). In brief, the conventional radiographic image seen at the output phosphor of an image intensifier is scanned by a high-resolution plumbicon television camera, and the video signal so generated is logarithmically amplified and then converted into digital form prior to storage in a computer. These image data are amenable to further processing and manipulation

There are several factors which reduce the image quality of DSA, the primary one being movement artefact. Immobilisation of the area under study and the gating of data acquisition by the R-wave of the electrocardiogram have both been used to produce good quality images more reliably following an intravenous injection In addition to the anatomical information, a timed sequence of digital images contains useful temporal information which hitherto has been largely ignored. A simple method of image processing is described which utilises this timing information and presents it as a colour-coded set of functional or parametric images.

The value of parametric imaging has been appreciated in relation to nuclear medicine data for some time. An example is the phase and amplitude analysis of gated blood pool radionuclide scans of the heart. Such an analysis enables dyskinesis and aneurysm formation to be evaluated scientifically, and the results are easily understood as a pair of images, colour coded to show the extent and timing of ventricular contraction on a pixel-by-pixel basis. One possible criticism of such an analysis, using nuclear medicine data, is the inherently low spatial resolution and, to a lesser extent, the need for gating in order to acquire sufficiently good statistics to provide raw images capable of analysis. Parametric imaging is not limited to nuclear medicine or radiology. Every image produced on a nuclear magnetic resonance (NMR) scanner is a true parametric image; the difference lies in that most NMR images are grey-scale coded in such a way as to mimic conventional computed tomography. Some workers are, however, now producing colour-coded NMR images. With NMR the parameters coded are the densities and relaxation times of the nuclei under study. Digital subtraction angiography shows the distribution and concentration of administered contrast medium. Despite the fundamental differences in data acquisition, the two imaging methods are similar (in respect of functional analysis) and may be considered together The key feature in all of these imaging methods is that the process of displaying the parametric data as an image renders underlying functional information easily recognisable.

The object of this paper is to describe a simple way to extract some important facts about each time–density curve and to display them as a set of parametric images which can be readily interpreted.

BACKGROUND AND METHOD

A 5F-gauge catheter is inserted into the superior vena cava via an ante-cubital vein and 40 ml of non-ionic contrast medium are injected at 25 ml/s. A timed series of unsubtracted or raw images is acquired over the region of interest with the patient in arrested respiration. Each image consists of a matrix of picture

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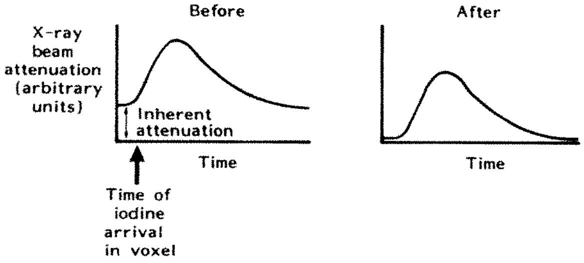

FIG. 1.

A typical time–density curve before and after subtraction of inherent attenuation.

elements (pixels) arranged in 512 lines each containing 512 pixels. The images were acquired using a Technicare DR960 DSA unit. The 512 × 512 matrices were compressed to 256 lines with 256 pixels in each line, to facilitate computation. The system computer, a Digital Equipment PDP 11/34A, was used to perform the calculations, and the images were displayed in colour on a Nodecrest nuclear medicine system running under MICAS.

Each pixel can take any value from 0 to 255; this number is a function of the attenuation of the X-ray beam by the tissue in a volume controlled by the depth of the patient and the pixel area. It may be appreciated that as the amount of attenuation in the voxel changes due to the passage of contrast material, so the pixel value will also change. The pixel value is at a maximum when there is little attenuation of the X-ray beam. As iodine flows through a voxel, the attenuation increases and the pixel value falls. It is this change of pixel value with time which forms the basis for our analysis.

Consider a single pixel in the matrix. Each image in the series will have a value in that pixel which depends on the inherent attenuation plus the amount of iodine present in the corresponding voxel. The first image in the series does not have any iodine present and so its pixel value represents only the inherent attenuation, which remains constant throughout the series. In order to determine the contribution to the pixel value due to the iodine present in any image, the inherent attenuation (or pixel value from the first frame) is subtracted from that pixel value. This is equivalent to subtraction of a mask image from contrast images if anatomical data only are to be reviewed in a cine fashion. It is more convenient to perform this "mask" subtraction on a pixel-by-pixel basis, as described, when generating parametric images. When this is done for a series of images, a curve is obtained for each pixel, which reflects the change, with time, in the amount of iodine present within the corresponding voxel. This curve is analogous to the time–activity curves of nuclear medicine. The pixel value is inverted to yield a conventional appreciation of change in density with respect to time; this is called the time–density curve (Fig. 1). In a typical study there are 64 images, each of which is composed of 256 × 256 (65 536) pixels. This yields 65 536 time–density curves, each curve having 64 data points (each data point corresponds to one image in the series). This amount of information in numerical form is difficult for an observer to assimilate, but presented as a colour-coded image, it becomes intelligible at a glance.

Before extraction of parameters, each curve is smoothed using a standard 3-point weighted running average, with weighting values of $\frac{1}{4}$, $\frac{1}{2}$ and $\frac{1}{4}$. The smoothing is performed at this stage to reduce the

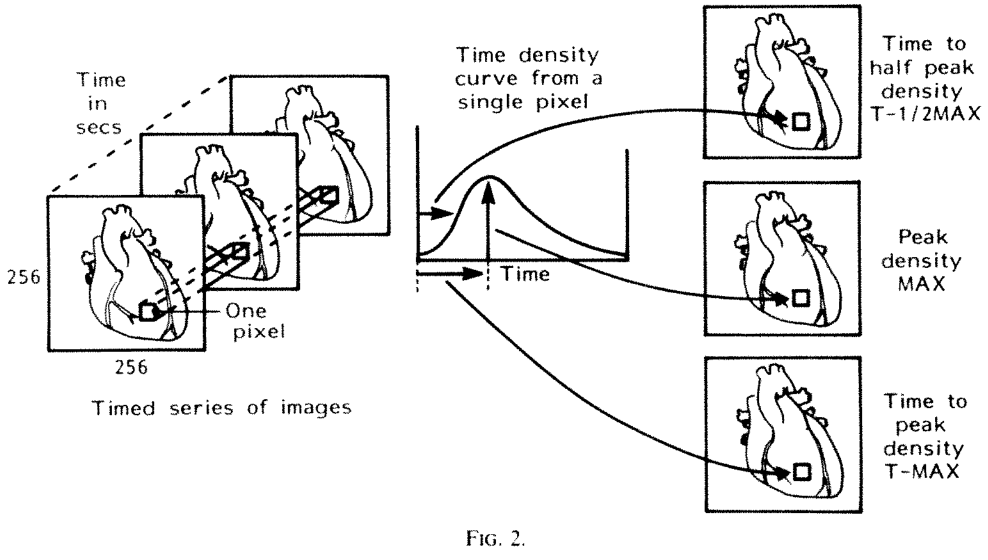
Time in secs
256
256
One pixel
Timed series of images
Time density curve from a single pixel
Time
Time to half peak density T-1/2MAX
Peak density MAX
Time to peak density T-MAX

FIG. 2.

The process of parametric analysis is illustrated from the initial image sequence to the three parametric images.

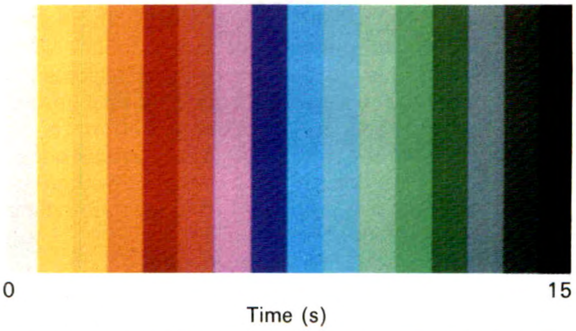

FIG. 3.
The colour time scale
used in the parametric images.

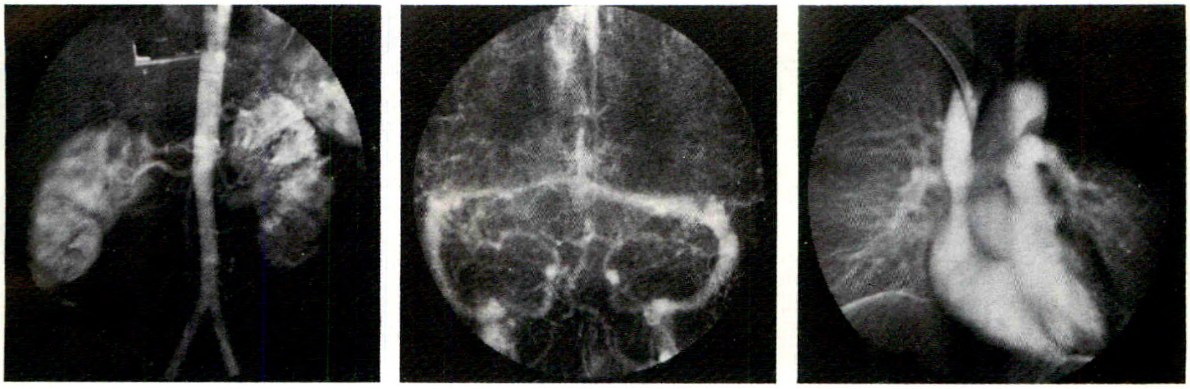

FIG. 4.

MAX images from three studies. (A) Bilateral renal study. (B) Occipito-frontal cerebral study from a patient with an occluded left carotid artery. (C) Cardio-pulmonary study from a patient with decreased perfusion to the left upper zone from a tumour compressing the left upper pulmonary artery.

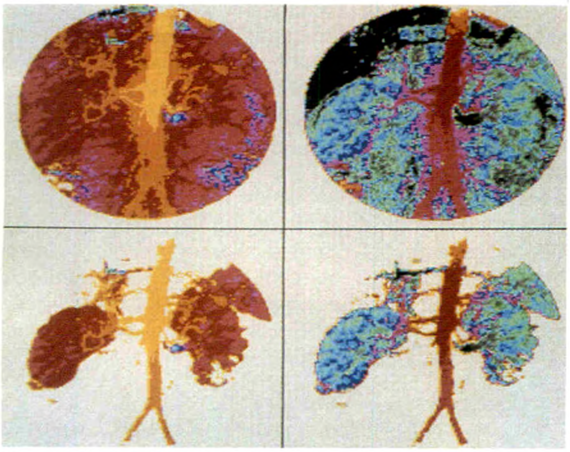

FIG. 5.

Colour-coded timing information from a bilateral renal study corresponding to the MAX image in Fig. 4A: (A) T-$\frac{1}{2}$ MAX and (B) T-MAX timing images obtained without a background cutoff; the kidneys are difficult to identify. Corresponding T-$\frac{1}{2}$ MAX (C) and T-MAX (D) images to (A) and (B) with a cutoff applied: the kidneys and spleen become clearly visible.

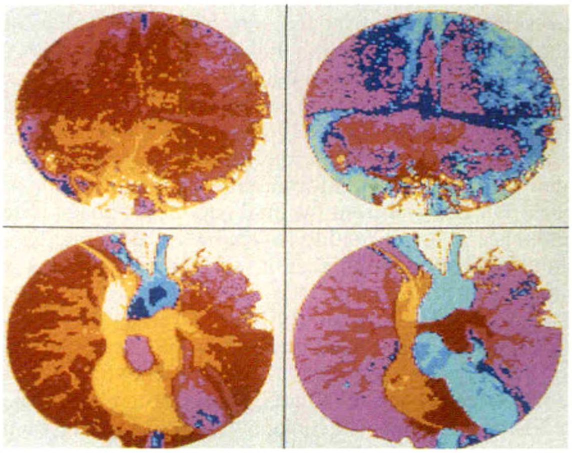

FIG. 6.

Colour-coded timing images from cerebral and cardio-pulmonary studies corresponding to the MAX images of Fig. 4B and Fig. 4C, respectively. (A) and (B) Timing information in a case of occluded left carotid artery: note that there is a difference of three colours between left and right parietal regions; this implies a 3 s delay in perfusion of the left parietal lobe. (C) and (D) Timing information in a case of compression of the left upper lobe pulmonary artery due to tumour: note the clear difference of six colours between the left and right ventricles, implying a 6 s transit time.

effects of errors resulting from slight variations ($\leqslant 5\%$) in X-ray intensity which occur from pulse to pulse during image acquisition. These variations lead to a "sawtooth" effect being visible on the time–density curves of unsmoothed data. The anatomical images are themselves never smoothed either temporally or spatially. The time information is precisely known, it does not suffer random or systematic error and it is not smoothed during our analysis. The smoothed curve is analysed and the peak value, time of occurrence of the peak value, and time of initial occurrence of half the peak value are calculated These parameters are called MAX, T-MAX and T-½ MAX respectively. Their calculation yields three values for each pixel in the image. Each value is stored in a separate matrix in the same pixel position as in the original image series; this process is summarised in Fig. 2.

The only pixels of interest are those where there is a significant change in iodine density with time. It is these pixels which constitute the major blood vessels and perfused organs in the image. Naturally, it is possible to generate a time–density curve for any pixel. If a pixel belongs to a background region of the image (and is therefore of little interest) its curve will not show a rise and fall; instead there will be a small monotonic rise in density (sometimes leading to a plateau), due to capillary vessel perfusion, with time. In most instances there is a significant difference between the peak value of these monotonic curves and the lowest peak value of the time–density curves generated from pixels within the regions of interest in the image Examining the set of anatomical images, a threshold value may be determined such that the majority of the peak values of the background pixels will fall below it. If the MAX value of a pixel does not rise above this threshold value, it is set to zero, as are the corresponding T-MAX and T-½ MAX values. This has the effect of minimising confusing data, due to background tissue perfusion, by removing the visual information generated by those background pixels from the final parametric image. The difference in image quality is demonstrated in Fig. 5. It should be appreciated that in some pixels there is a small contribution to the pixel value from the background tissue perfusion which overlies the organ under study. This small contribution has been ignored for the purposes of our analysis. The attenuation due to iodine is calculated to a first approximation only. The characteristics of the image intensifier, television camera, and analogue-to-digital converter are matched by the manufacturer, and are all assumed to be linear over the range of data in the clinical situation. No correction is made for spatial variation (*e.g.*, pincushion effect), veiling glare or beam hardening. Temporal and spatial smoothing of the final parametric image is not undertaken

The MAX image contains purely anatomical information and is best viewed with a conventional grey scale. The T-MAX and T-½ MAX images contain only timing information, and the values may be coded on a colour scale with good effect. We have used a colour scale in which each colour represents a period of 1 s Other colour scales may readily be implemented and differences in time down to 0.1 s are demonstrable.

Examples of images obtained together with the time scale used are illustrated in Figs. 3–6; a bilateral renal study with and without background masking, a cerebral study and a cardio-pulmonary study are shown.

Discussion

Digital subtraction angiography was able to provide simultaneously both anatomical and functional information. Hitherto, the emphasis has been on structure. Functional information is concerned with the assessment of iodine concentration and its variation with time. Absolute measurement of iodine concentration is difficult because scatter, beam hardening and veiling glare lead to a non-linear relationship between iodine concentration and pixel value. However, if only relative changes in iodine concentration are needed, then these problems do not arise (Riederer et al, 1981, Shaw et al, 1982).

In the parametric images presented, the MAX image, while giving anatomical information, also enables direct comparison of maximum iodine concentration to be made between different areas of the image, irrespective of when that maximum occurs. The T-½ MAX image, colour coded for time, provides an estimate of the first time of arrival of contrast material to an organ. The T-MAX image allows peak-to-peak transit times to be measured. At first glance, there would appear to be no benefit in calculating both T-½ MAX and T-MAX; however, in certain circumstances the tissue under investigation alters the shape of the time–density curve so that it becomes wider at half maximum. This would lead to a discrepancy in transit times calculated by the two parameters. This discrepancy may vary in different pathological states and provide a method for distinguishing them.

Timing information is displayed using a colour scale for ease of identification of small differences. The same scale is used for all studies, thereby enabling direct comparison between patients, as well as between different studies on the same patient It is possible to expand the colour scale to allow changes in time of 0.1 s to be easily determined.

Conclusion

We have presented a simple method, requiring modest computer facilities, for extracting relative iodine concentration, time of maximum iodine concentration and time to half maximum iodine concentration from a timed sequence of DSA images. The parameters enable an estimate of organ perfusion to be made as well as measurement of peak-to-peak transit times in blood vessels. Changes in the shape of the time–density curves may also be evaluated from these parameters. Work is in progress to evaluate the clinical usefulness of this technique in the renal, neurological and cardio-pulmonary fields.

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Book reviews

Radiocontrast Agents, Handbook of Experimental Pharmacology, Vol. 73 Ed. by M. Sovak, pp. xvi+609, 1984 (Springer-Verlag, Berlin), DM.490.00.
ISBN 3-540-13107-8

It is surprising, given the great interest in iodinated radiological contrast agents in the last few years and the considerable scientific activity engendered, that few books should have appeared on the subject. This multiauthor volume, running to some 600 pages, goes a long way towards filling the gap. It is actually Volume 73 in the series "Handbook of Experimental Pharmacology", but it is much more readable than its full title would suggest. A survey of the list of contributors, which include Almén, Golman, Higgins, Lasser and Sovak, suggest a stimulating read and the book, on the whole, does not disappoint. The first two chapters on contrast-agent chemistry offer far more detail than the great majority of radiologists would ever need or want, but they constitute an excellent and authoritative reference source to answer any question that could conceivably arise. There are chapters on cardiovascular, urological and neurological applications of contrast agents, each with considerable, but readable, information on the pharmacology and toxicology of these systems and a background of the relevant physiology.

For those who want to do research, there are several sections on techniques for the investigation of these organ systems and a chapter on anaesthesia in experimental animals. For completeness, there are chapters on mechanisms of adverse reactions by Lasser, and even one by Nelson, asking whether contrast agents are mutagenic (yet another thing to worry about!).

Those with a special interest in contrast agents will want this book for themselves. Those with an interest in neuroradiology, uroradiology or cardiac radiology would benefit from reading relevant chapters and all radiologists would find it a helpful book for occasional reference. It would therefore, be a useful addition to departmental libraries.

PETER DAWSON

Abdominal Ultrasonography, 2nd edit. Ed. by B. B. Goldberg, pp. 528, 1984 (John Wiley & Sons, New York), £54.45.
ISBN 0-471-08569-3

The first edition of this book under the title *Abdominal Gray Scale Ultrasonography* was published in 1977. This second edition incorporates much new material but the size and wide-ranging content of the book have obviously necessitated a fairly prolonged period of gestation. Many of the chapters are illustrated almost exclusively by static images, including those in which the text repeatedly emphasises the advantages of real-time scanning. Despite this criticism the individual authors have approached their subjects with care and have gathered large numbers of references up to and including 1981. One can assume that the editing phase took three years; considerable progress has been made during that intervening interval.

As with most multiauthor books the standard and polarity of presentation of the images is very variable but the content of the text is sufficiently good to make this a useful reference book.

A novel introduction is the chapter on normal and abnormal bowel, an area in which most of us feel ultrasound has little to offer. This chapter serves to prove that the frontiers of diagnostic ultrasound continue to be pushed towards and will certainly encourage the reviewer not to be so dismissive of requests for intestinal ultrasound examination.

HYLTON B MEIRE

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Ultrasound of the hip: a review of the applications of a new technique

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(*Received February 1985*)

ABSTRACT

In an attempt both to reduce gonadal irradiation incurred with conventional radiology, and to image the unossified structures of the neonatal hip, several groups have undertaken studies on aspects of hip ultrasound particularly with reference to the paediatric patient. The ultrasound anatomy of the unossified infant hip has been described by Graf in Austria The same author has devised an ultrasonographic classification for hip dysplasias and dislocations which has gained widespread acceptance in mainland Europe

Two studies have appeared exploring the use of ultrasound for the measurement of femoral neck anteversion but as yet these have not been compared with CT or trigonometric methods of assessment

Ultrasound has been shown to be effective in the detection of hip joint effusions, but its role in the management of the "irritable hip" has yet to be defined

Research into this little-known application of ultrasound has been appearing in the world literature since 1979 The authors' interest in this technique was stimulated by the large number of children attending the Royal National Orthopaedic Hospital for monitoring of Perthes' disease and congenital hip dysplasias. In the years from diagnosis to maturity dozens of radiographs are obtained of their hips and any possibility of replacing at least some of these by ultrasound would be welcomed

A review of the literature showed that little work has been published in English and even less has appeared in radiological journals.

This review attempts to illustrate important aspects of recent work and where appropriate, comments have been made in the light of the authors' own experience of this technique.

The following headings are convenient, although several of the papers cover more than a single topic:

1. Ultrasound anatomy of the hip;
2. Determination of femoral neck anteversion;
3. Detection of joint effusion;
4. Assessment of congenital hip dysplasia and dislocation.

ULTRASOUND ANATOMY OF THE HIP

Almost every article, whatever the application, has contained a description of arthrosonographic anatomy of the hip. This is usually demonstrated in coronal section with the probe held lateral to the hip joint above the greater trochanter. In their pioneering article, a small section of which was devoted to the hip, Kramps & Lenschow (1979) observed that the cartilaginous labrum could be imaged. Independently Seltzer et al (1980) produced a study on arthrosonography of the hip, shoulder and elbow. Their approach to the anatomy of the adult hip was directed towards a comparison with CT scanning, identifying several muscle groups in transverse section. They also dwelt on the appearance of the joint capsule for the purpose of identifying joint effusions Wilson et al (1984), describing the detection of effusions, included a useful sectional diagram of the hip to aid the interpretation of the sonographic images.

Undoubtedly the most comprehensive accounts of the ultrasound anatomy of the infant hip have been the result of the work by Graf in Austria. Two accounts (Graf, 1981, 1982a) detail waterbath experiments on a disarticulated femur and acetabulum utilising a static scanner.

Graf found that hyaline cartilage structures did not produce detectable echoes whereas fibrocartilage produced weak echoes. Neither the water/cartilage interface of the experimental femoral head nor the cartilaginous component of the acetabulum could be imaged unless coated with a plastic membrane. In contrast, Novick et al (1983) found that the femoral head, when imaged with a real-time transducer, produced weak echoes. Novick comments on an anechoic triangle adjacent to the bony acetabular roof, of whose nature they are uncertain. Graf has identified this as the unossified acetabular roof (Fig. 1A).

Graf utilises a German architectural term "Erker", which literally means "bay" (as in bay window), to describe the lateral aspect of the roof of the acetabulum as seen in an anteroposterior radiograph. On the "bony bay" rests the hyaline cartilaginous "bay" from which hangs the fibrocartilaginous labrum (Figs 1A). The size of the hyaline cartilage bay can be inferred by the anechoic gap between the echogenic fibrocartilaginous labrum and the totally reflective iliac bone (Graf, 1982a). This important observation will be discussed in depth in the section on hip dysplasias.

Graf identifies the defect in the acetabulum caused by

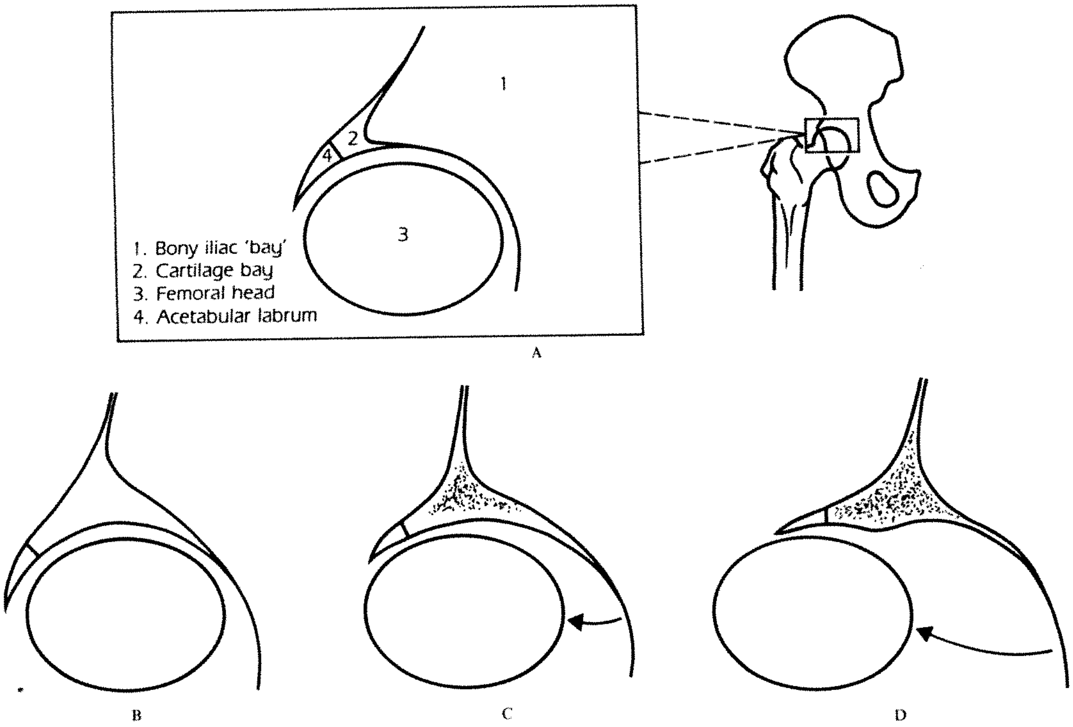

FIG. 1.
After Graf.
Diagrammatic representation of ultrasonographic types.
(A) Type I. (B) Type II. (C) Type IIIB. (D) Type IV.

the Y cartilage. Novick et al observed this landmark but again were uncertain of its true nature. Both groups identify the ossific nucleus as an echogenic structure within the femoral head. Graf (1983a) and Schuler & Rossak (1984) reported that this echogenic region was detectable before the radiological appearance of the ossific nucleus.

As the femoral epiphysis ossifies, the ultrasonographic appearance begins to resemble the adult hip which is very different in appearance (Fig. 2). Here the totally reflective femoral head obscures deep views of the acetabulum. This fact has moved Graf to state that "to his knowledge the technique has no practical application in the adult hip" (Graf, 1983b), a point on which we differ strongly.

Graf's three most concise accounts of normal anatomy are published in German (Graf, 1982a, 1982b, 1983b) but papers in English are also available (Graf, 1980, 1981, 1983a). These detail the structures one can expect to visualise, together with their ultrasonographic characteristics. Figs. 2 and 3 illustrate the typical appearance of the normal adult and infant hips.

DETERMINATION OF ANTEVERSION OF THE FEMORAL NECK

Moulton & Upadhay (1982) devised a static B-scanning technique for measuring femoral neck anteversion. They describe a waterbath study on 30 "dry" femora suspended in a gantry which simultaneously measures the required angle. Their clinical study on 18 volunteers involves scanning the knee anteriorly to determine the intercondylar plane and then, with the leg immobilised, scanning along the femoral neck, the two images being displayed on the same photographic record and the angles calculated with a protractor.

Zarate et al (1983) ingeniously modified this technique for use with a real-time linear array apparatus by attaching a spirit level to the transducer, eliminating the problem of a real-time image always appearing in the same position on the monitor regardless of the position of the transducer. In their waterbath experiment using Moulton and Upadhay's gantry, they economised on femora by sectioning a single specimen at midshaft. By rotating the fragments independently, they produced any angle of anteversion they wished.

Moulton and Upadhay's approach images the patella anterior to the condyle and is only suitable for static scanning. The technique of Zarate et al produces an image of the posterior contour of the femoral condyles. Zarate et al assume the tangent to the condyles to be the intercondylar plane, whereas Moulton and Upadhay utilise a deep bony landmark more in keeping with CT methods of assessment of anteversion.

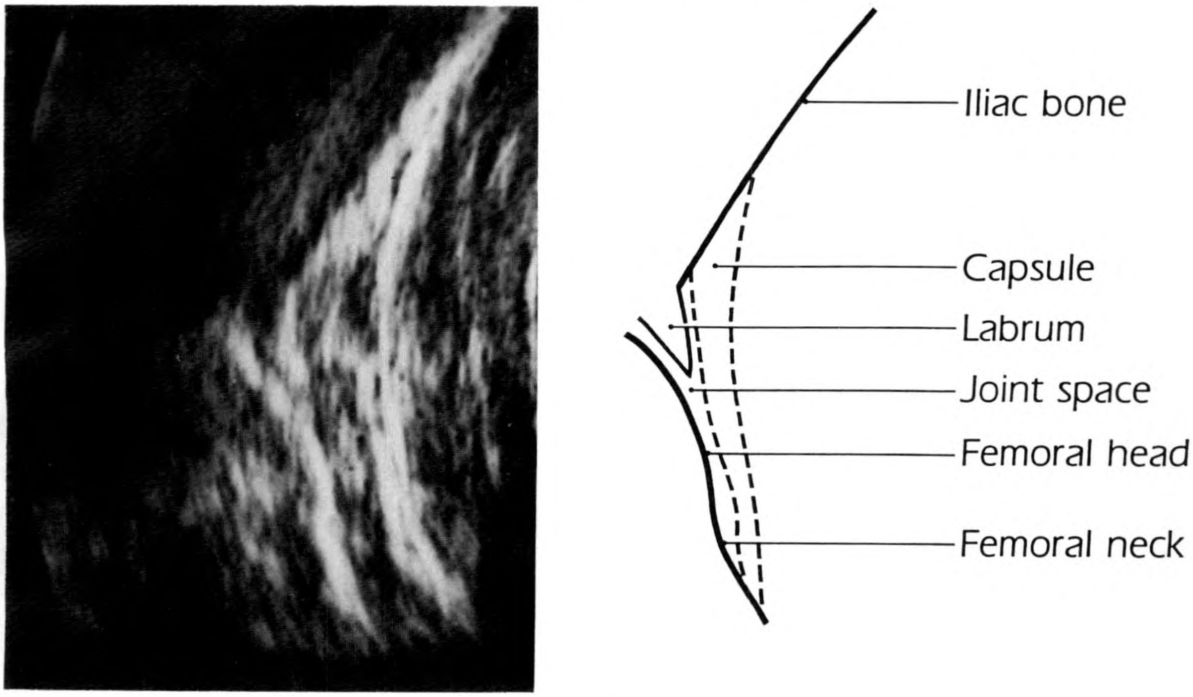

FIG. 2.

Ultrasonograph of adult hip, transducer positioned to produce a view similar to Fig. 1.

While we would agree that both methods are appealing, both on account of their availability and absence of ionising radiation, both groups assume, however, that accurate results obtained under direct vision in a waterbath imply that the method is reliable *in vivo*.

DETECTION OF EFFUSIONS

In their account of the ultrasound anatomy of the hip, Seltzer et al (1980) included a study on four patients with "iatrogenic effusions" produced by intra-articular injection of contrast medium or local anaesthetic. They suggested that a hypoechoic halo between the highly reflective capsule and femoral head is seen in the presence of an effusion, but is not seen in its absence (Fig. 2). We consider them to be incorrect concerning the absence of this hypoechoic rim unless an effusion is present. Their illustration of a normal hip shows the halo quite clearly.

Wilson et al (1984) confirmed effusions in 13 out of

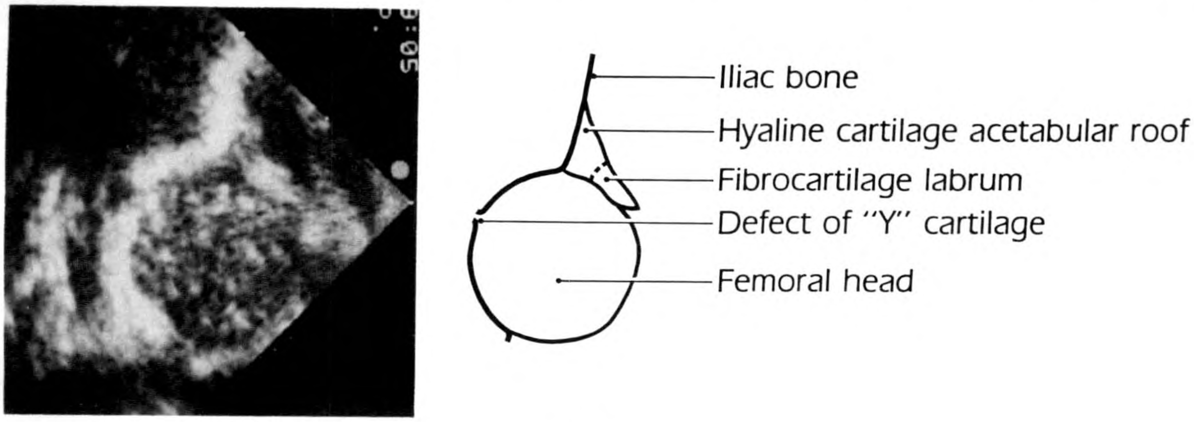

FIG. 3.

Ultrasonograph of term neonate, transducer positioned to produce a view similar to Fig. 1. This is a Type I hip.

15 patients in whom it was ultrasonographically suspected. Their criterion for an effusion was an increase of more than 3 mm of this hypoechoic halo compared with the asymptomatic hip.

We have found that this echo-free zone between capsule and head is due at least in part to the articular hyaline cartilage surrounding the femoral head. This is increased in dysplastic hips where the cartilage depth is excessive.

The smallest identifiable effusion remains speculative. While Wilson et al did not attempt to estimate this, Novick et al (1983) claim, from observations on a single post-mortem study of an infant, that the intra-articular injection of as little as 1 ml was detectable as an anechoic halo surrounding the cartilaginous femoral head. In a further study on a term baby, a suspected effusion failed to be confirmed by aspiration. In contrast, Wilson et al (1984) found cadaveric studies difficult because of dehydration and gas within the soft tissues.

Seltzer et al (1980) state that a 14 ml collection produces a 7–9 mm halo, while a 10 ml collection creates a 2 mm rim between capsule and femoral head In our experience a 2 mm rim is normal. We have routinely been performing post-arthrographic ultrasound at the Royal National Orthopaedic Hospital for the last year and have not confidently been able to detect the small volumes of contrast we regularly use (about 5 ml).

While we believe ultrasound is useful for detecting effusions, it has raised the question of what action to take following its detection. Wilson et al (1984) comment that in 12 of their 30 patients the result altered the clinical management. While they do not state the age range of their series, the majority of ours are children with irritable hips, most of which resolve without complication. Perthes' disease or septic arthritis are the main sinister developments.

If, like Kemp (1981), one believes that any effusion predisposes to avascular necrosis by reducing the blood flow to the femoral head, logically one would drain all effusions. This view, however, has not been widely accepted by clinicians.

CONGENITAL DISLOCATION AND HIP DYSPLASIAS

We believe this to be the most significant application of hip ultrasound. It is interesting to follow the work of Graf from 1980 His first paper (Graf, 1980) described the diagnosis of congenital dislocation using a static scanner. Following the publication of his experiments on the ultrasound anatomy of the hip (Graf, 1981, 1982a), Graf's ideas on hip dysplasias evolve into a fascinating ultrasound classification (Graf, 1983b, 1983c, 1984). The most sophisticated accounts (1983c, 1984) include both morphological and geometrical criteria for his classification.

Graf's *Type I* is the normal appearance with a well-formed bony acetabular roof with an easily identifiable lateral margin. The hypoechoic cartilaginous "bay" is elongated inferolaterally and the echogenic fibrocartilaginous labrum extends from this, adequately encompassing the femoral head (Fig. 1A)

The *Type II* hip shows a rounded, less developed bony bay with a larger cartilaginous component extending inferolaterally (Fig. 1B). Once again, the femoral head is well covered by the acetabulum.

Although the ratio of cartilaginous to bony acetabular roof is increased, this is a *normal* hip—what Graf calls "delayed ossification". This acetabulum would appear dysplastic on a radiograph but Graf states that given time the hyaline cartilage will ossify and Type II will become Type I without treatment (Graf, 1982b).

Type III. Here the femoral head is displaced laterally producing deformation and pressure on the cartilaginous bay. Quoting Oelkers' work, Graf divides Type III into Subtypes A and B. Apparently Oelkers has shown histologically that the border between hyaline cartilage and bone changes under pressure, producing accumulations of chondrocytes and fibrils (Oelkers, 1981). This produces an unusually echogenic cartilaginous bay: Graf calls these changes of echo pattern "compression zones" Hence Subtype IIIA—lateral displacement and deformation of cartilaginous bay with normal echoes; Subtype IIIB—lateral displacement and deformation with increased echoes in the cartilaginous bay, indicating internal histological derangement of the cartilage (Fig. 1C). Later Graf mentions, but does not substantiate, that the hips with echogenic compression zones have a poorer prognosis.

Type IV. These are either the appearances of minimal contact between femoral head and acetabulum or total dislocation of the hip (Fig. 1D)

This phenomenon of late ossification of the acetabular margin is not a new observation. Schuler and Rossak quote a publication by Faber (1938) where he clearly showed this arthrographically. Schuler and Rossak give an account of their experience with Graf's classification and include several useful case reports documenting the ultrasound progress of dysplastic hips They include a case, clinically normal, detected by ultrasound on routine "well baby" examination, implying that ultrasound is more accurate than "click testing" (Schuler & Rossak, 1984).

Brockmann et al (1984) published a trial comparing ultrasound, radiology and clinical diagnosis in 34 hips (17 children) using both real-time and static scan images. This trial has several weaknesses, not least of which is the absence of any eventual confirmation (*e.g.*, arthrographic) of any of the diagnoses. Nevertheless, they conclude that ultrasound has reached the level of radiology and "to some extent has overtaken it" A useful suggestion in Brockmann's paper is a system for recording the ultrasound images of the hip in a manner acceptable to clinicians, almost giving the impression of a frontal pelvic radiograph

The study of Novick et al (1983) utilises a very different technique with an additional mediolateral view, an approach which Graf found difficult to perform and to interpret (Graf, 1980). Using a 5 MHz real-time transducer, Novick found the unossified femoral head to be weakly echogenic, in contrast to the anechoic appearance described by Graf. This may enable them to define its position more accurately. They state that the mediolateral view is the only possible approach when the child is wearing a plaster spica. We have attempted this on several children in abduction splints without success. As mentioned above, Novick et al observed the triangular hypoechoic structure of the cartilaginous acetabular roof but did not recognise its true identity. They concluded that normal hips are easy to identify but the absence of anatomical landmarks makes definition of the abnormal hip difficult.

Graf has suggested that the current X-ray geometric criteria for diagnosing a dysplastic hip be abandoned altogether and suggests the term "ossification retardation" for Type II hips.

If Graf is correct, this classification, particularly Type II, is of outstanding importance corresponding as it does to the radiographic appearance of dysplastic acetabula with increased acetabular angles. When recognised, these children may be placed in an abduction splint for several weeks, at the end of which it is assumed, wrongly, that this is responsible for a normal pair of acetabula in a child who, in fact, did not require treatment in the first place. At worst, as a result of the treatment, the child may develop avascular necrosis in a hip that would have developed normally if left alone, a point emphasised by Brockmann et al.

Schuler and Rossak's experience is based on 1500 hips, while Graf's is culled from 3000 examinations although it would appear that Graf confirmed the diagnoses arthrographically in only six living and four post-mortem studies.

Graf and Schuler have introduced ultrasound as a routine screening method at their respective institutes in Austria and Germany. Even if the value is accepted, there is simply no possibility of providing a routine nursery screening service at present in Great Britain, but selective screening of "high risk" infants may be a reasonable alternative.

The possibility that we may be inappropriately treating a group of patients is nevertheless extremely alarming. At the very least, careful ultrasound examination of radiologically dysplastic acetabula should be attempted in infants until the existence of Graf's Type II hip is either confirmed or refuted.

Notwithstanding the hyperbole of some of the enthusiasts, we would subscribe to Schuler's modest claim that "ultrasound is a worthwhile addition to our diagnostic options . . . not merely an unfocused radiograph".

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Book reviews

Assessment of Skeletal Maturity and Prediction of Adult Height (TW^2 Method) By Tanner, Whitehouse, Cameron, Marshal, Healy, Goldstein, pp. 108, 1984 (Academic Press, London), $49.50/£33.00
ISBN 0–12–683360–5

The determination of skeletal maturity "bone age" has an important place in the practice of paediatrics, especially in relation to endocrinological problems and growth disorders. This is the first statement in the preface and can be regarded as the apologia for this book There are five chapters in which the measurement of maturity, the definition and scoring of the bone stages, the standards for skeletal maturity, the prediction of adult height and the hormonal control, and clinical applications are discussed. The authors describe the different systems of determining bone age and then explain the development of the weighted system· the TW^2 method.

There is an excellent discussion of population differences in skeletal maturity and the importance of this in the interpretation of bone ages is stressed.

The chapter on the prediction of adult height has been almost completely rewritten since the first edition, and revised height predictions are given which the authors regard as being more accurate. Replacement of the first edition by this second edition is therefore important.

The chapters are followed by three appendixes describing the rating system. The radiographs which depict the varied stages in the development of the individual bones are satisfactory and the supporting line-drawings and text are clear and easy to follow. The TW^2 method of calculating bone age is based on the allocation of a score, which has a different weighting for the sexes, to each of 20 epiphyses in the hand and carpus The score is totalled and the age is then read by comparing the total with charts This method undoubtedly is less subjective than many other methods of calculating bone age. It is still subject to some observer bias, because it can sometimes be difficult to decide upon the stage of development, but with experience of the system, reliability increases. It is time consuming, even with experience, each rating will take 5–7 minutes if it is carefully done. The system is, therefore impractical as a routine method in a busy paediatric hospital, and must perforce be reserved for those children with special problems, such as growth-hormone deficiency, or where the prediction of adult height is important.

Routine bone age assessment using an atlas such as Greulich and Pyle is satisfactory in most patients *Assessment of Skeletal Maturity and Prediction of Adult Height* is an essential bench book in departments of paediatric endocrinology and auxology, and in the X-ray departments associated with these clinics, but its sale is likely to be limited to these departments. Radiologists are unlikely to want a personal copy or to regard the book as light bedside reading; it is, however, an important contribution to the management of children with growth problems and is the result of over 20 years clinical experience It is fascinating reading for those concerned with the care of these children and the authors must be congratulated on making such a complex subject understandable.

H. CARTY

Doppler Echocardiography Ed. by N C Nanda, pp. viii + 522, 1985 (Igaku-Shoin, Tokyo, New York), £61.75
ISBN 0–89640–102–2

Although introduced over 10 years ago, Doppler techniques have not been widely applied to intracardiac blood flow until recently, when reports that trans-valvar pressure gradients can be estimated from peak blood-velocity measurements have stimulated a tidal wave of interest in the method.

The appearance of this comprehensive treatment of the subject by Dr Nanda and his colleagues is thus very timely. The book includes sections on the physical principles of Doppler instrumentation, the Doppler examination, applications in acquired heart disease, applications in congenital heart disease, and evaluation of fetal haemodynamics, plus several appendices.

The section on physical principles is good, providing clear explanations of complex concepts, but the chapters on clinical applications can only be described as a muddle There are constant repetitions of basic concepts by the various authors, even the same illustration and caption are repeated on at least one occasion. Aortic stenosis, for example, is included under adult valve disease, in an introductory section to congenital heart disease, and in the section on Doppler findings in congenital disease (which opens with a discussion of aortic regurgitation). The congenital disease section covers topics such as surgical details of the Mustard operation, the relevance of which to Doppler techniques is hard to see Similar confusion exists in the indexing; casual references, for example, to trisomy 21, are cited, but there is no reference to normal velocity values, although two tables exist, each with differing figures

One can forgive some repetition in a multiauthor text covering a rapidly evolving specialty, but to find it to such an extent is surprising as Dr Nanda is both editor and co-author of over half the chapters

Such is the need for teaching material on Doppler techniques that I expect this book will sell, despite the problems described. I hope this will encourage Dr Nanda to undertake a thorough revision and to tighten up the editorial control, so that a future edition can become a really useful text.

GRAHAM J. LEECH

1986, *The British Journal of Radiology*, 59, 19–24 JANUARY 1986

Clinical comparison of a new technetium 99m DTPA aerosol delivery system with krypton 81m

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ABSTRACT

We compared the clinical performance of a new ^{99}Tc^{m} DTPA aerosol delivery system with steady-state ^{81}Kr^{m} gas in the diagnosis of pulmonary embolic disease. Forty patients had aerosol and ^{81}Kr^{m} ventilation imaging followed by perfusion scintigraphy. The combined aerosol/perfusion images were compared with ^{81}Kr^{m}/perfusion images for diagnostic equivalence. Aerosol image quality was also compared directly with ^{81}Kr^{m}.

Three-quarters of the patients who had segmental ventilation-perfusion (V/Q) mismatch on ^{81}Kr^{m}/perfusion images also had mismatch on aerosol/perfusion images. Of those who had no mismatch on Kr/perfusion images, it was possible to rule out mismatch on aerosol/perfusion images in 80% of cases. Fifteen per cent of aerosol images were uninterpretable due to excess deposition in large airways. This problem was significantly more frequent in smokers than in non-smokers. The average delivery efficiency of the system was 2%, in terms of the proportion of loaded activity retained in the lungs.

We conclude that the new device gives accurate clinical information in most cases, but is of less value for smokers.

It has been well established that ventilation imaging greatly improves the specificity of lung perfusion scintigraphy in suspected pulmonary embolic disease (Alderson et al, 1976; McNeill, 1976; Neumann et al, 1980). However, satisfactory agents for ventilation imaging are not widely available. The agents currently in use are radioactive gases, none of which is ideal. ^{81}Kr^{m} gas produces high-quality images (Fazio & Jones, 1975; Lavender & Cunningham, 1980) but, because the parent ^{81}Rb has a short half-life, it is limited to centres within easy reach of a cyclotron. ^{133}Xe gas, although more generally used, produces images which are not strictly comparable with perfusion images and may cause local atmospheric contamination. ^{127}Xe, a cyclotron-produced radionuclide, has more desirable imaging characteristics than ^{133}Xe, but is expensive and also presents problems of disposal.

In 1965, Taplin and Poe described a method of lung imaging with inhaled radioaerosols. Since then, several test agents have been studied, including ^{99}Tc^{m} pertechnetate, ^{99}Tc^{m} sulphur colloid, ^{113}In aerosol and ^{99}Tc^{m} DTPA (Taplin & Chopra, 1978). Pertechnetate is rapidly cleared from the lungs after inhalation, and currently-available nebulisers do not deliver the agent quickly enough to give an adequate count rate. Sulphur colloid remains in lung macrophages for longer than the physical lifetime of ^{99}Tc^{m}, making subsequent perfusion imaging difficult and increasing the lung radiation burden. ^{113}In^{m} has a suitable half-life (100 min) and a high gamma ray energy (392 keV) which enables post-perfusion scintigraphy to be carried out. It has been shown by Fazio et al (1982) to produce high quality images but is unlikely to be widely used since few departments have this agent available. Attention has therefore been re-focussed on ^{99}Tc^{m} DTPA which is the agent originally described by Taplin and Poe in 1965.

Twenty years on, some fundamental problems associated with radioaerosol imaging have not been resolved. Chief amongst these are the low efficiency with which nebulised activity is retained in the lung and the tendency for inhaled particles to impact in central airways. Smaller particles are less likely to become deposited in the proximal bronchial tree (Newman et al, 1982) and efforts have been directed to reducing particle size. Most commonly the output from a jet nebuliser has been directed into a large settling bag, allowing larger particles to gravitate out of the air stream (Fazio et al, 1982, Hayes et al, 1979). However, settling bags are cumbersome and difficult to shield.

No compact aerosol delivery system has been generally available until recently. Buxton-Thomas and Wraight (1984) and Royston et al (1984) described their initial experience with an aerosol imaging system capable of generating small particles of ^{99}Tc^{m} DTPA and their results were quite promising. This paper concerns the clinical evaluation of a commercially available delivery system† which differs in design from the device described by Buxton-Thomas and Wraight (1984). The aerosol system does not contain a reservoir and uses a different technique of particle separation from that described by Royston et al (1983).

MATERIALS AND METHODS

Forty adult patients with suspected pulmonary embolic disease were studied using the SynteVent device. Informed consent was obtained in all cases prior to the

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†SynteVent Aerosol delivery system, Synaco, Palo Alto, Calif.

procedure. In 37 of these patients a smoking history was available: 15 were smokers (or had been smokers within a year prior to the study) and 22 were non-smokers. The forced expiratory volume in one second (FEV$_1$) was measured in 37 patients and the predicted FEV$_1$ based on age, sex and height was estimated in each case.

The delivery device used consists of a plastic jet nebuliser to which is fitted a manifold with a breathing hose and a bacterial filter. The nebuliser contains a reservoir for the liquid, a Venturi tube connected to a gas source and a series of baffles which act as droplet traps. An aerosol is created when gas flowing through the nebuliser draws liquid from the reservoir by the Venturi effect and shears it into droplets. The larger particles are trapped by the baffles which allow the smaller particles to pass on. Once trapped, the larger particles coalesce and gravitate back into the reservoir.

The particle size distribution at the outflow from the device was studied in two laboratories using different sizing techniques. An Electrostatic Classifier (EC) was used in The Desert Research Institute Laboratory in Nevada. Here, the Volume Mean Diameter (VMD) was calculated. The VMD refers to a particle size calculated from the volume of the particle; in this case measured from the size-dependent voltage change on the EC. The workers quote a VMD of 1.7 μm and a modal diameter of 1.15 μm. A cascade impactor was used in St. Joseph's Hospital, McMaster University, Ontario. The technique is based on the principle that particles cross airstreams and impinge on collector plates in a fashion dependent on particle mass. Using this method, the workers in Ontario found a Mass Median Aerodynamic Diameter (MMAD) of 0.57 μm, with a geometric standard deviation (σ_g) of 1.34. The MMAD is a dry-weight measurement, and is defined such that half the mass of the particulate system is contained in particles having an aerodynamic diameter less than this value. Numerically, the distribution is weighted in favour of particles smaller than the MMAD, and 98% of the particles have an aerodynamic diameter less than 1 μm. The workers quote a geometric standard deviation because the size distribution is skewed; $\sigma_g < 1.1$ corresponds to monodispersion of the particles. The authors would point out that they did not themselves measure the particle size distribution, and that, in practice, the size distribution in the airways may differ significantly from values measured in the laboratory. Factors such as humidification and variations in gas flow rates (Alderson et al, 1984) may increase the effective size of the inhaled particles.

The patients inhale the aerosol through a mouthpiece and one-way valves within the manifold direct exhaled gas through a filter to the environment. Excess aerosol is thus trapped in the device and does not contaminate the surroundings. The entire system is efficiently shielded in lead. The device was loaded with 1000 MBq (30 mCi) ^{99}Tc^{m} DTPA in 3 ml saline. The gas flow rate was set to 8 l/min and the patients inhaled the aerosol in a sitting position for approximately six minutes; none appeared distressed by the procedure. Images were acquired in standard views up to 250K counts per image on a large field-of-view gamma camera interfaced to an MDS A^2 computer. This was immediately followed by steady-state ^{81}Kr^{m} inhalation in the same views (using the 190 keV energy window) and 60 min later by perfusion imaging using 75 MBq (2 mCi) ^{99}Tc^{m} MAA. At this time background lung activity due to inhaled ^{99}Tc^{m} had fallen to less than 10% of that due to injected ^{99}Tc^{m}

The efficiency of the system was estimated by comparing the count rate due to aerosol retained in the lung with the count rate due to the subsequent injection of a known dose of ^{99}Tc^{m} MAA, all of which was assumed to be trapped in lung capillaries. Delivery efficiency was calculated in over 20 patients with widely varying lung function.

Data Analysis

Aerosol and krypton images were compared for technical quality and diagnostic equivalence. In order to simplify the comparison, krypton was used as a standard and it was assumed for purposes of the study that the combined V(Kr)/Q images gave accurate information in all cases. The patients were divided into two groups; those who had segmental V/Q mismatch (or greater) and those who did not. The calculated sensitivity and specificity of the combined aerosol/Q studies represent the degree to which they reflect V/Q mismatch seen on V(Kr)/Q images. It is stressed that

TABLE I

Ventilation/perfusion (V/Q) mismatch

	All patients		Non-smokers		Smokers	
	V(Kr)/Q+	V(Kr)/Q−	V(Kr)/Q+	V(Kr)/Q−	V(Kr)/Q+	V(Kr)/Q−
V(Aer)/Q+	6	0	5	0	1	0
V(Aer)/Q−	1	26	0	15	1	9
Aerosol unhelpful	1	6	0	2	1	3
Sensitivity %	75		100		33	
Specificity %	81		88		75	
Agreement %	80		91		66	

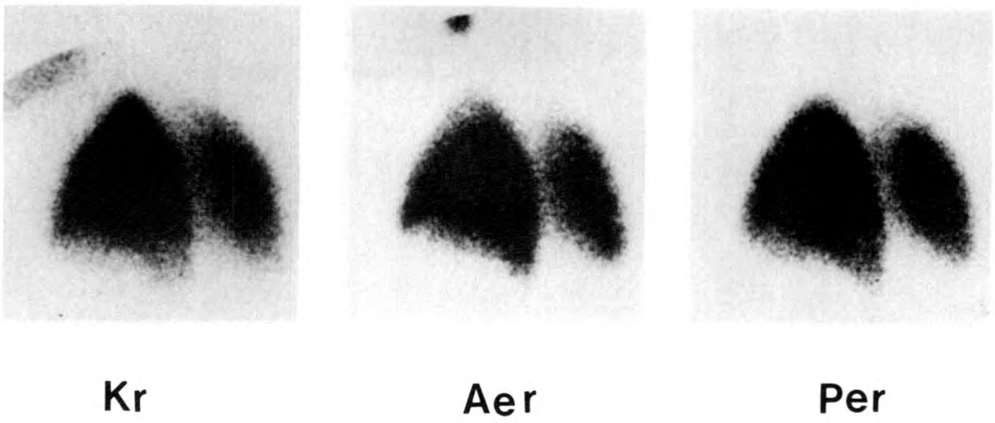

FIG. 1.

A normal aerosol study; left posterior oblique view. The activity in the pharynx is quite characteristic. This may subsequently appear in the stomach after swallowing.

these values are not absolute, as angiography was not performed in any case, and are intended only to give a figure of merit relative to $^{81}Kr^m$. Aerosol and krypton images were also compared separately from the perfusion images to assess how faithfully aerosol reflected the distribution of $^{81}Kr^m$. Discrepancies between sets of images were noted visually and no digital processing was performed.

Three grades of deposition of aerosol in central airways were defined as follows:

0 = no abnormal deposition
1 = some abnormal deposition but activity seen in all regions ventilated on krypton images
2 = abnormal deposition with no counts in some regions ventilated on krypton images.

RESULTS

The results are shown in Tables I and II and Fig. 5.

Representative images are shown in Figs 1–4. Twenty-one patients had no abnormal airway deposition, 12 had Grade 1 deposition and seven patients had Grade 2 deposition. Despite a degree of spottiness in the images, those with Grade 1 deposition were correctly interpretable. Those with Grade 2 deposition were in general regarded as uninterpretable. Of the seven patients with Grade 2 deposition, five were smokers, but the association is not statistically significant. The frequency of abnormal airway deposition was significantly higher in smokers than in non-smokers ($p < 0.005$) and in patients whose FEV_1 was less than 50% predicted ($p < 0.001$).

The overall sensitivity of the combined aerosol V/Q images relative to krypton was 75% and the specificity 81%. There was agreement in 80%. Among 22 non-smokers, the sensitivity was 100% and the specificity 88% with agreement in 91%.

All ten patients in whom the aerosol and krypton images were abnormal and equivalent had matched V/Q defects only. In none were there matched defects in association with unmatched defects in the same study. The eight patients who had V/Q mismatch with krypton had aerosol scans which were normal in six cases, uninterpretable in one, and potentially falsely negative in one. For all patients studied the krypton images were of high quality.

In five patients, aerosol defects were greater than krypton defects. In one of these patients, it was thought that perfusion was more defective than ventilation on the krypton image but less impaired than ventilation on the aerosol image. If one accepts that krypton is giving the correct diagnosis, that is a larger defect of perfusion than ventilation indicative of pulmonary infarction, then the combined aerosol V/Q study yields a false negative diagnosis. This is equivalent to a false negative rate of 2.5%. The efficiency of the delivery system was estimated at a mean of 2%, with a range of 1–4%.

TABLE II

AEROSOL VS $^{81}Kr^m$

Pattern	No. of patients
Kr = Aerosol = Normal	19
Kr = Aerosol = Abnormal	10
Aerosol defects > Kr defects	5
Aerosol uninterpretable	6
Kr uninterpretable	0

DISCUSSION

The pattern of distribution of inhaled radioaerosol may give meaningful information about lung pathophysiology. Impaction in central airways may reflect turbulent airflow and/or airway narrowing. This phenomenon is influenced by the pattern of breathing, and penetration of aerosol to the small airways may be

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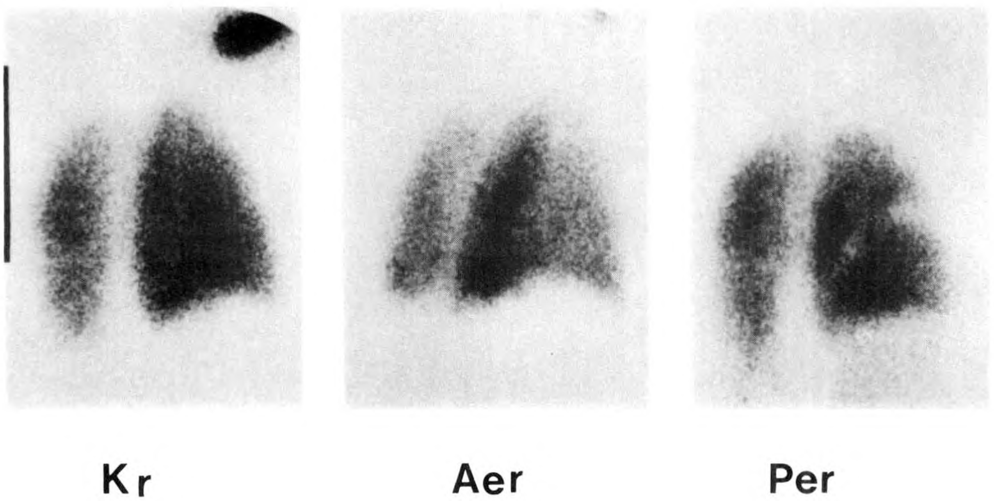

FIG. 2.

Ventilation/perfusion mismatch; right posterior oblique view. Note the perfusion defect in the right upper lobe (one of many in this patient) which appears normally ventilated on aerosol and Kr-81m images. Excess deposition of aerosol is seen around the right hilum (grade I) but the study is still diagnostic.

increased by using slow respiratory flow rates and large tidal volumes and pausing for a few seconds at end-inspiration (Pavia et al, 1977). The use of helium as a carrier gas should, in theory, diminish central airways deposition by decreasing turbulence. No such manoeuvres were employed in the present study as the delivery system was being tried for routine clinical use.

The signal from steady-state inhalation of a gas with a long half-life is dependent on the volume of lung ventilated and is independent of regional lung time-constants, since all ventilated areas will reach the equilibrium concentration. The signal from inhaled aerosol particles which are not deposited by turbulence on airways would be similar to an inhaled single breath. This differs from the steady-state of $^{81}Kr^{m}$ where the count rate is influenced by regions of high specific ventilation (Fazio & Jones, 1975). The images therefore would be expected to differ to a minor extent particularly in signals coming from dependent parts of the lungs (Alderson et al, 1984).

A second cause for an image due to an aerosol differing from that due to $^{81}Kr^{m}$ might be states

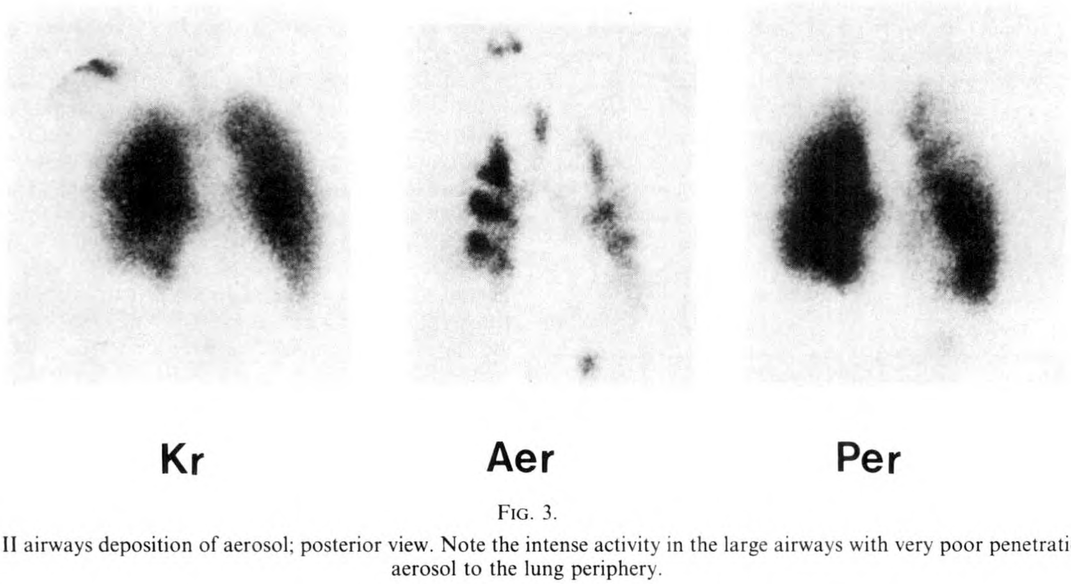

FIG. 3.

Grade II airways deposition of aerosol; posterior view. Note the intense activity in the large airways with very poor penetration of aerosol to the lung periphery.

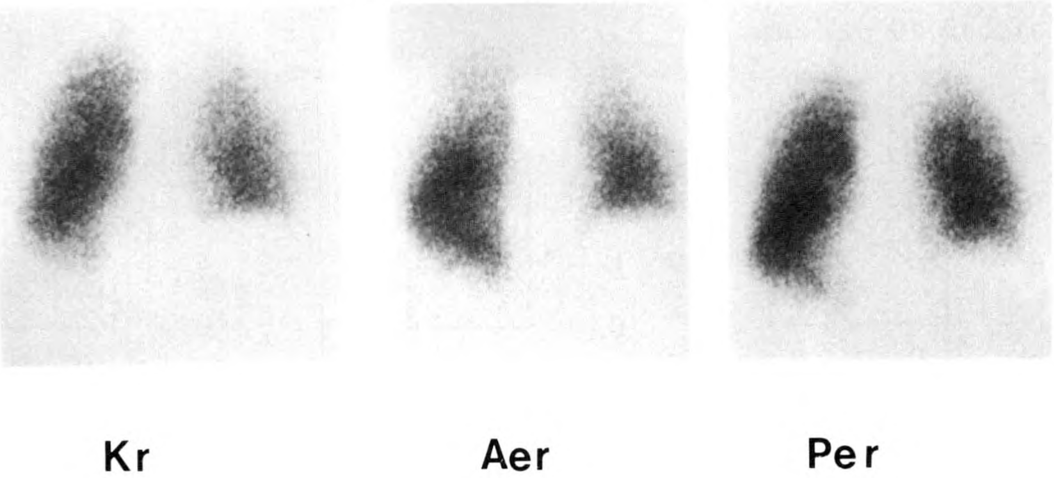

FIG. 4.

A matched defect is seen in the right base; posterior view. A pleural effusion was visible on the chest radiograph.

involving collateral ventilation where the diffusion of a gas might occur but particles remain deposited in situ. This phenomenon might result in a ventilatory defect appearing larger with the use of an aerosol than with the image with steady-state ^{81}Kr^{m}.

There are theoretical advantages and practical problems in using ^{99}Tc^{m} for both ventilation and perfusion studies. Similar depths of lung are imaged and the detection system gives images of comparable resolution. However, since discrimination on an energy basis is impossible, other methods must be used to minimise cross talk between ventilation and perfusion images. There are a number of ways to approach the problem. An attractive method is digital subtraction of one image from the corresponding composite image. This technique is, however, dependent on reproducible positioning and requires specialised software. Another approach is to "swamp" the ventilation counts with a much higher count density due to injected ^{99}Tc^{m}. This is limited by dosimetric considerations. A third approach is to wait until inhaled activity has fallen to an acceptable level. We used this last method and found it quite satisfactory. In theory, clumping of particles in conducting airways in the presence of impaired mucociliary clearance may cause troublesome retention of activity but we did not find this a problem.

The twin problems of central airways deposition and low efficiency remain to be resolved. The particle size distribution generated by the SynteVent device is satisfactory for patients with normal airways or mild airways obstruction, but patients with more severe disease will require smaller particles to inhale. In order to achieve this with conventional nebulisers, it is likely that output would be made to drop to lower levels. The efficiency of the delivery system, calculated at 2% is low. There is, however, a theoretical upper limit to efficiency using the present breathing circuits, determined by the fractional retention of aerosol in the lungs per breath. Davies et al (1972) studied the fate of 0.5 μm aerosol particles during steady breathing and found that, on average, 90% of the inhaled aerosol was recovered in the exhaled air. Since all exhaled radioaerosol is trapped in the expiratory filter, a maximum of 10% of nebulised activity would be retained in the lungs. In order to increase efficiency above this level a rebreathing method would be necessary whereby exhaled aerosol is channelled back into the reservoir of the nebuliser. If delivery efficiency could be significantly improved, then perhaps ^{99}Tc^{m} pertechnetate can be delivered to the lungs in quantities sufficient to yield adequate images. The rapid removal of pertechnetate from the lungs would then considerably shorten the delay between aerosol inhalation and subsequent perfusion imaging.

Alderson et al have recently (1984) published the results of a multi-centre radio-aerosol trial using the same device. They compared aerosol with ^{133}Xe in 81 patients and with ^{81}Kr^{m} in 26 patients. They found that aerosol compared favourably with both ^{133}Xe and ^{81}Kr^{m} and concluded that they were diagnostically equivalent. We found that, on the whole, aerosol performed less well than ^{81}Kr^{m} and although our data analysis differs from theirs in potentially significant respects, the incidence of uninterpretable aerosol images in our experience was notably higher than theirs (15% vs 6%). Alderson et al (1984) made the interesting observation that the signal from dependent parts of the lung is relatively stronger with aerosol than with gas. We observed the same phenomenon, which we feel is readily explicable on the basis of the high specific ventilation found in dependent lung regions. For a given total ventilatory turnover, high values of ventilation per unit of lung volume diminish signal intensity from steady-state ^{81}Kr^{m} (Fazio & Jones, 1975), whereas aerosol would suffer no such degradation.

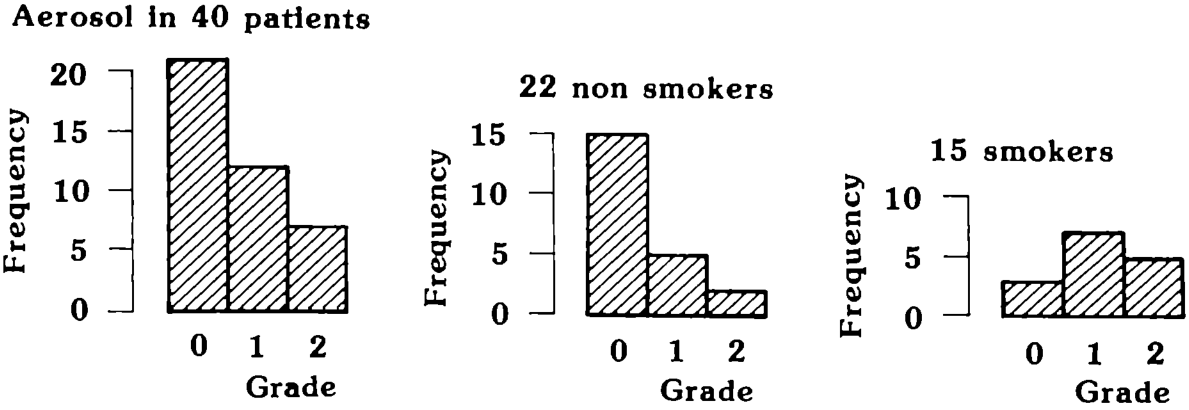

FIG 5

Grade and frequency of central airways deposition of aerosol in the study group and two sub groups

In conclusion, we feel that the new device gives useful information in most patients. Among non-smokers its performance is comparable to ^{81}Kr^{m} although in smokers it is less reliable. It should prove to be a practical alternative to ^{133}Xe as an adjunct to perfusion scintigraphy.

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Focal sparing in fatty infiltration of the liver

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ABSTRACT

Four cases of focal sparing in otherwise diffuse fatty infiltration of the liver are reported. The characteristic features are described as shown at sonography, computed tomography (CT) and scintigraphy. It is emphasised that, with ultrasound, if the increased echogenicity of the majority of the liver is not appreciated, then the area of normal hepatic parenchyma may be misinterpreted as a pathological hypoechoic lesion.

Fatty infiltration of the liver occurs in response to various toxic and metabolic insults. It may affect the whole liver or it may assume a non-uniform or patchy distribution. The non-uniformity may be so marked that the fat is deposited only in one or more well-circumscribed regions or, alternatively, discrete areas of parenchyma may remain uninvolved when the rest of the liver is diffusely infiltrated with fat. These two conditions, focal deposition and focal sparing, may create diagnostic problems for the radiologist, surgeon and pathologist by simulating mass lesions of a more sinister nature.

Focal deposition has been well demonstrated by various imaging techniques (Brawer et al, 1980; Halvarsen et al, 1982) but we feel that the presence and significance of focal sparing has not been similarly emphasised. Four cases seen in a six-month period at the Royal Marsden Hospital are therefore reported in order to draw attention to the condition, describe its characteristic appearances and illustrate the diagnostic problems its presence creates. Each case was initially detected sonographically as a relatively hypoechoic discrete area. Scintigraphy was used for further investigation in all cases, computed tomography (CT) was performed in three and open biopsy was carried out in one.

CASE REPORTS

Case 1

A 49-year-old woman presented to another hospital with acute onset of diabetes mellitus. Seven days later she developed obstructive jaundice and laparotomy was performed. At operation, the distal common bile duct was found to be compressed by the pancreatic head, the whole pancreas was bulky and there were several enlarged peripancreatic lymph nodes. In addition, whilst the heavily bile-stained liver was uniform on inspection, there was one area in the posterior aspect of the right lobe which was of different texture on palpation. A clinical diagnosis of carcinoma of the pancreas, with hepatic and lymph node metastases, was made. However,

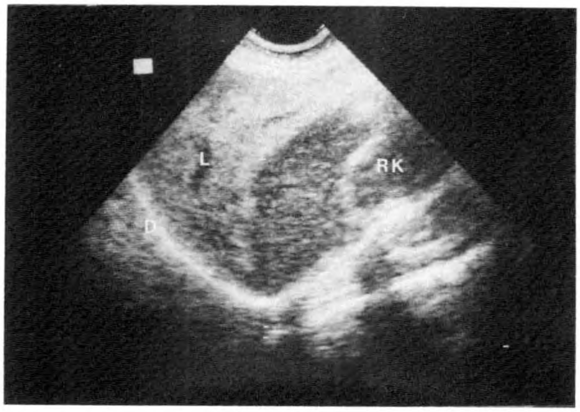

FIG. 1A.

Longitudinal ultrasound scan through the right hypochondrium. Focal sparing is seen as a well-defined region of relative hypoechogenicity in the posterior subcapsular aspect of the right lobe of the liver. D = diaphragm; RK = right kidney; L = liver.

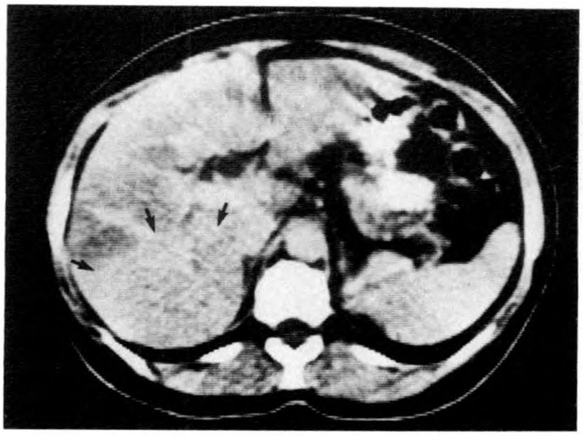

FIG. 1B.

CT examination performed three days after ultrasound, showing an area of normal parenchyma in the posterior aspect of the right lobe of the liver (68 HU) whilst the rest of the liver is of reduced attenuation and demonstrates prominent vascularity consistent with fatty infiltration (mean 32 HU).

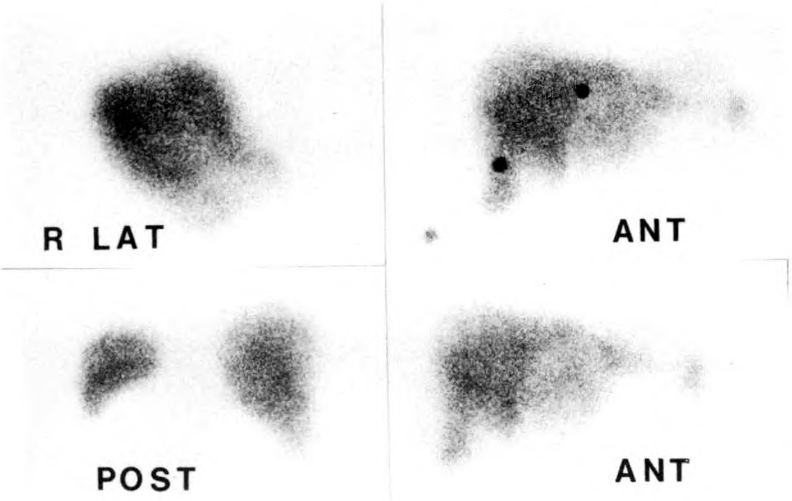

Fig. 2.

Uniform uptake of ^{99}Tc^{m}-labelled sulphur colloid is seen throughout the liver and spleen.

histological examination of the lymph nodes showed reactive change only and a biopsy of the abnormal region of the liver revealed cholestasis with no evidence of other pathology. Despite these negative findings pancreatic carcinoma was still considered to be the most likely diagnosis and the patient was therefore referred to this hospital for further investigations.

Amongst other examinations abdominal ultrasound was performed. This demonstrated a hypoechoic uniformly enlarged pancreas consistent with acute pancreatitis and showed a fine bright echo pattern in the majority of the liver suggestive of fatty change. However, in the posterior subcapsular aspect of the right lobe of the liver, corresponding to the region of altered texture found at laparotomy, there was a well-defined geographical area, 4 cm in diameter, of relatively reduced reflectivity (Fig. 1a). Review of the pre-operative CT scan showed the reduced density of fatty change throughout the liver (mean 32 HU) but with normal appearances in this region in the right lobe (68 HU) (Fig. 1b). Liver scintigraphy at this time had been normal with no evidence of a focal defect (Fig. 2). The patient was thus diagnosed as having acute painless pancreatitis with obstructive jaundice due to oedema of the pancreatic head, as well as diabetes-related fatty infiltration of the liver with focal sparing of part of the right lobe.

The patient has now been followed up over nine months and has remained well. The pancreas is showing a gradual return to normal dimensions and her insulin requirement has fallen. The liver function tests are normal and the fatty infiltration of the liver has resolved completely. During this period, ultrasound proved more sensitive than CT in detecting the residual fatty change and hence the focal sparing. The CT density readings had returned to within the normal range nine weeks after presentation whilst ultrasound showed characteristic abnormalities for a further six weeks (Figs. 3a, b, 4).

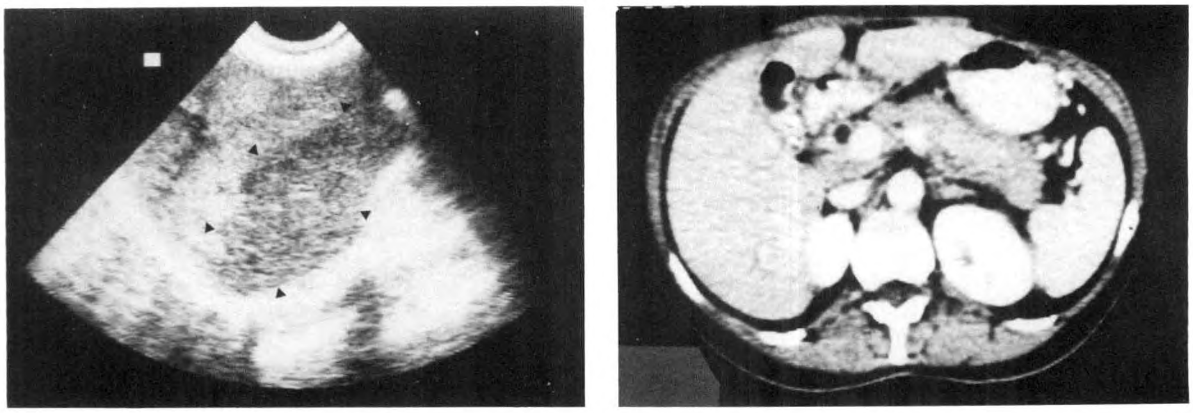
(a) (b)

Fig. 3.

Ultrasound (a) and contrast-enhanced CT (b) examinations performed on the same day nine weeks after presentation. Ultrasound clearly demonstrates fatty infiltration of the liver with the area of focal sparing in the right lobe (arrowed). However, the CT appearances and density readings are now uniform throughout the liver and are within the normal range (L37 W256). Air is seen within the gallbladder as a result of the cholecystoenterostomy performed at the time of laparotomy.

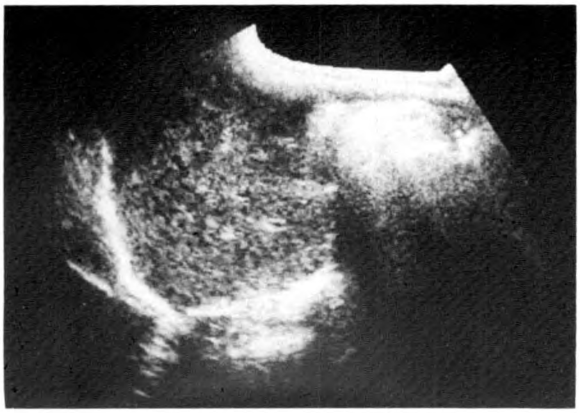

FIG. 4.

Longitudinal ultrasound scan through the right hypochondrium performed six months after presentation. Fatty infiltration of the liver and focal sparing is no longer detectable.

Case 2

During staging investigations prior to therapy for a right-sided testicular seminoma, a 36-year-old unemployed dockworker was found to have elevated liver enzymes (alkaline phosphatase 157 iu/l, alanine transaminase 30 iu/l and gamma-glutamyl transpeptidase 73 iu/l). He admitted to heavy alcohol intake. At ultrasound, the majority of the liver returned a fine, bright echo pattern consistent with fatty change but a well-defined area of lower echogenicity, 3 cm in diameter was identified posteriorly in the left lobe (Fig. 5). Scintigraphy, however, showed uniform colloid uptake throughout the liver with no evidence of a focal defect. A CT scan was therefore performed. This confirmed the impression of fatty change by demonstrating reduced density in the majority of the liver (mean 35 HU). The well-defined focal area in the posterior aspect of the left lobe was shown to be of higher density (62.9 HU) and therefore consistent with normal hepatic parenchyma (Fig. 6).

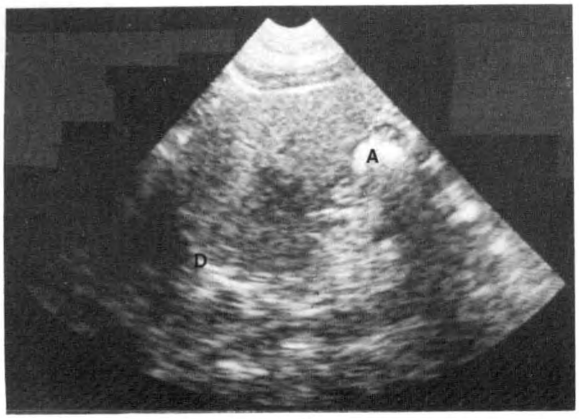

FIG. 5.

Longitudinal ultrasound scan through the epigastrium. Focal sparing is seen as an irregular shaped area of reduced echogenicity in the left lobe of the liver. D = diaphragm; A = gastric antrum.

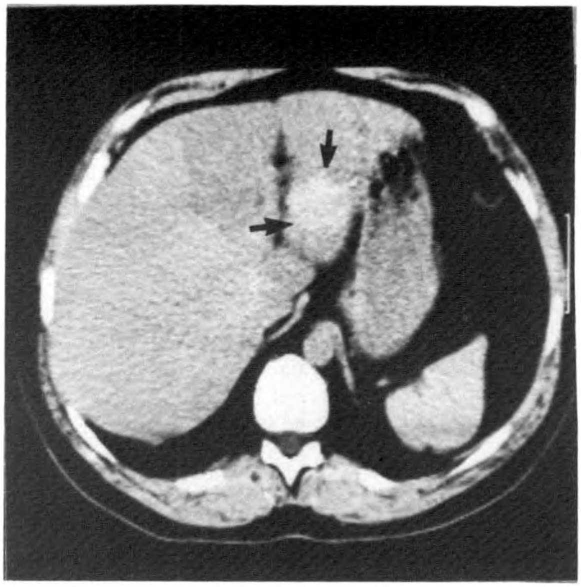

FIG. 6.

CT scan shows an area of normal hepatic parenchyma (focal sparing) posteriorly in the left lobe whilst the surrounding liver demonstrates the reduced attenuation of fatty change. The majority of the right lobe shows less severe fatty infiltration (L27 W134).

The patient has remained well with Stage 1 testicular disease over a six month follow-up period. The findings are consistent with alcohol-related fatty infiltration of the liver with sparing of part of the left lobe.

Case 3

A 76-year-old woman was referred for liver ultrasound after routine clinical examination revealed a smooth enlarged liver. Hepatic enzymes were normal. She had been taking up to 20 mg prednisolone daily for the previous five years for giant cell arteritis with eye complications.

Ultrasound revealed a fine, bright echo pattern consistent with hepatic fatty infiltration but with a well-defined region of lower level echoes, 7 cm in diameter, in the right lobe. There was a normal and uniform distribution of colloid on scintigraphy and the appearances were thus felt to be consistent with steroid-induced fatty infiltration of the liver and focal sparing of part of the right lobe. Over the past eight months the patient has remained well apart from developing polymyalgia rheumatica with bilateral hand-shoulder syndrome.

Case 4

A 56-year-old man complained to his general practitioner of increasing abdominal girth. In view of his history of significant regular alcohol intake the patient was referred for ultrasound. This revealed no evidence of ascites but the liver returned a fine bright echo pattern consistent with fatty infiltration. There was a clearly defined geographical area 3 cm in diameter returning relatively low-level echoes in the left lobe of the liver.

Scintigraphy showed uniform isotope uptake throughout the liver and CT confirmed that the density of the geographical region in the left lobe was consistent with normal liver whilst the remainder showed reduced density suggestive of fatty change. The appearances on CT scanning were only visible using a narrow window width whereas the ultrasound abnormalities were much more readily identified.

DISCUSSION

Fatty infiltration of the liver is most frequently seen in association with alcoholism but it is also described in obesity, nutritional deficiency, diabetes mellitus, after jejuno-ileal bypass surgery as well as in patients receiving steroids, intravenous hyperalimentation and hepatoxic drugs. The normal liver contains up to 5% fat by weight but this may rise to 40–50% as droplets of triglycerides accumulate in the hepatocytes (Alpers & Isselbacher, 1975).

Non-uniformity of fatty change can create diagnostic confusion, particularly in the case of diffuse infiltration with focal sparing. In these circumstances, if the increased echogenicity of the majority of the liver is not appreciated at ultrasound examination, the area of normal parenchyma may be interpreted as a hypoechoic focal lesion (Scott et al, 1980). It is thus liable to be mistaken for a metastatic deposit, a primary neoplasm, an abscess or other disease.

There are several features which may help to distinguish between focal sparing and pathological lesions. Focal sparing has a characteristic position and appearance; it is a well-defined subcapsular lesion with geographical margins and is segmental or lobar in distribution. It shows no mass effect either by displacement of vascular branches or by deformity of the liver contour. At scintigraphy, diffuse fatty infiltration with focal sparing will characteristically show uniform colloid uptake throughout the liver. Coincidental cirrhosis may cause some patchiness of isotope activity (Meek et al, 1984) but in neither circumstance will there be any evidence of a photon-deficient area corresponding to the sonographic abnormality. This is because the uptake of colloid reflects Kupffer cell activity and is unaffected by changes in the fat content of the hepatocytes.

CT may be helpful in confirming the ultrasound impression of fatty infiltration because there is a strong inverse correlation between CT number values and liver triglyceride concentration (Bydder et al, 1980). The technique, however, is sometimes less sensitive than ultrasound in detecting minor degrees of fatty change. For example, we found that during the resolution of the fatty changes in Case 1 the CT numbers and appearances had returned to within normal limits whilst characteristic sonographic abnormalities were still present. This is because liver with a fat content of up to 10% still has attenuation values which lie within the range for normal liver parenchyma (50–80 HU) (Bydder et al, 1980).

Fatty infiltration of the liver is often rapidly reversible after withdrawal of the toxic insult. Follow-up examinations may therefore be diagnostic by demonstrating a return of the normal echogenicity of the liver and thus a disappearance of the discrete area of focal sparing. Alcohol-related fatty change has been shown to resolve histologically 6 to 31 days after alcohol withdrawal (Weber & Rubin, 1968; Bashist et al, 1982).

In summary, when an apparent mass lesion is identified in the liver it is important to consider the diagnosis of focal sparing in diffuse fatty infiltration. The characteristic sonographic appearances, CT density readings and the absence of scintigraphic abnormalities should provide sufficient evidence to make a confident diagnosis. It must be remembered that biopsy of this region will reveal normal liver parenchyma only.

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Diverticular disease (adenomyomatosis) of the gallbladder: a radiological–pathological survey

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ABSTRACT

Seventy consecutive gallbladders removed at surgery were examined radiologically and pathologically. Fifteen (21%) of the operative specimens showed naked-eye changes of adenomyomatosis. The main conclusions drawn from this study are that this abnormality is present in a much higher proportion of gallbladders removed at surgery than is generally realised, and that the pathogenesis is primarily an abnormality of muscle contractions, with a strong similarity to diverticular disease of the colon. Diverticular disease of the gallbladder might well be the most appropriate name for this condition. The results of a post-operative clinical assessment of patients with diverticular disease are also presented. But this represents a small number of patients and larger, perhaps multicentre, surveys would be required in order to assess the clinical significance of this interesting abnormality.

Extensions of the mucosa (Rokitansky–Aschoff sinuses) into and through the muscle wall are common findings on examination of operative specimens of the gallbladder. In some cases the mucosal extensions are marked and occur in association with local thickening of the muscular layer, which produce a lesion visible to the naked eye. This combination of mucosal and muscular change has been recorded in the literature under a wide variety of names: cholecystitis glandularis proliferans, adenoma, adenomyomatosis, hamartoma, myoepithelial anomaly, or diverticulosis of the gallbladder.

The lesion is common and has been recognised radiologically in 5% of oral cholecystograms (Jutras et al, 1960; Fotopoulos & Crampton, 1964). It was described in only 7% of two hundred autopsies (Bricker & Halpert, 1963) but this was a retrospective study. It can occur in the absence of gallstones. Radiological detection of diverticular disease raises the problem whether such gallbladders should be removed in order to relieve symptoms (Berk et al, 1983; Jutras et al, 1960; Fotopoulos and Crampton, 1964; Bevan, 1970; Heald, 1970; Davies, 1971).

This study presents the detailed pathological, radiological and clinical findings in 15 patients with diverticular disease in whom local thickening of the wall was prominent enough to be seen macroscopically.

PATIENTS AND METHODS

Seventy consecutive patients who had a cholecystectomy for standard indications, such as attacks of right hypochondrial pain, jaundice, and fatty dyspepsia, were studied. The gallbladders were received in the laboratory fresh and unopened. Bile was removed by needle aspiration and the lumen filled to a firm consistency with a mixture of water-soluble contrast medium and 10% formol-saline. After 24 h fixation the gallbladder was opened following radiography of the operative specimen. Fifteen showed localised lesions of the wall visible to the naked eye. In addition the presence of stones, cholesterolosis and intraluminal polyps were recorded. Standard blocks were examined from the fundus, body and neck of each gallbladder, as well as from any macroscopic lesions noted on examination. Paraffin sections were stained with haematoxylin and eosin, elastic Van Giesen and Mason's trichrome. Frozen sections were stained with Oil-red-O. Eleven patients with diverticular disease (four others defaulted) and a group matched with gallstones for age, sex and time since operation were interviewed by a surgeon (P.S.), who did not know the pathological findings. Symptoms before and after operation were recorded on a standard questionnaire. The patients were questioned regarding acute symptoms and also symptoms between attacks. The findings were analysed to determine whether there was any difference in mode of presentation, or response to cholecystectomy.

RESULTS

Radiology

Radiographs of the operative specimens showing diverticular disease are shown in Fig. 1. Segmental strictures (Fig. 2B) were seen in the body or neck and were usually single, although occasionally more than one was present. They varied in length from a few millimetres to 2 cm, and were usually easy to recognise on the oral cholecystogram. In 12 patients with opacifying gallbladders at oral cholecystography, five of seven strictures were seen pre-operatively. Fundal nodules were sometimes seen as the classically described

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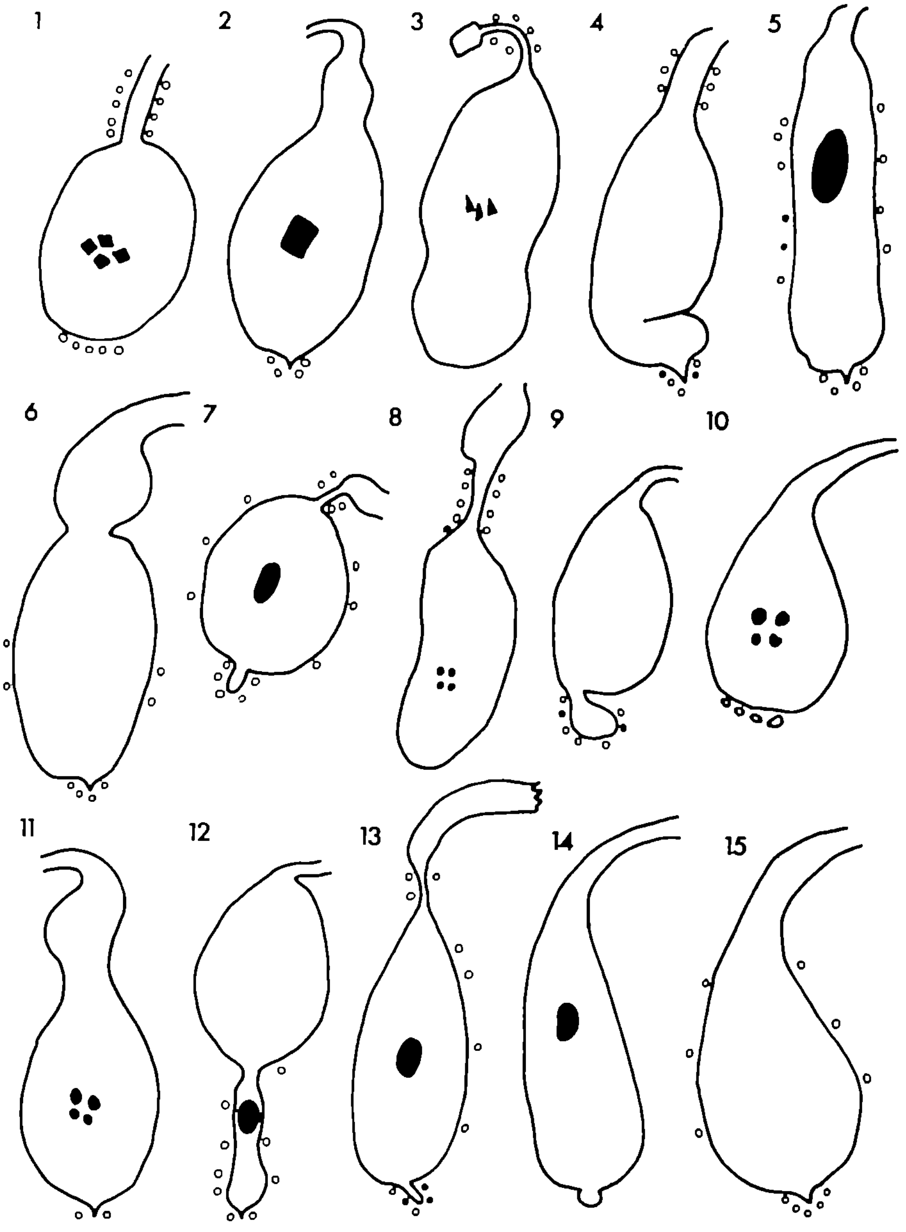

FIG. 1

Composition of the post-operative radiological and pathological findings in the 15 cases of diverticular disease Stones are indicated by intraluminal symbols Case 4 has a fundal nodule in the loculus of a Phrygian cap.

pointed spike surrounded by a ring of contrast-filled sacs (Fig. 2c). Much more commonly, the sacs or the point did not fill sufficiently well with contrast medium to be seen, and a flattened fundus was the sole indication of a fundal nodule. Nodules co-existed with strictures (Fig. 1: Cases 6, 7 and 13) or were found alone (Fig. 1: Cases 2, 4, 5, 14, 15). In this series there were eight nodules but only three were diagnosed on oral cholecystography. There were no examples of diverticula without an associated stricture or fundal nodule It is important to note that mild strictures are appreciated only when the gallbladder is distended A gallbladder opened by the surgeon after operation will make diagnosis of this condition very difficult.

Pathology

The patterns seen on macroscopic examination of the opened gallbladder in the patients with diverticular disease are shown in Fig. 1. The histological features were of epithelial diverticula extending from the lumen

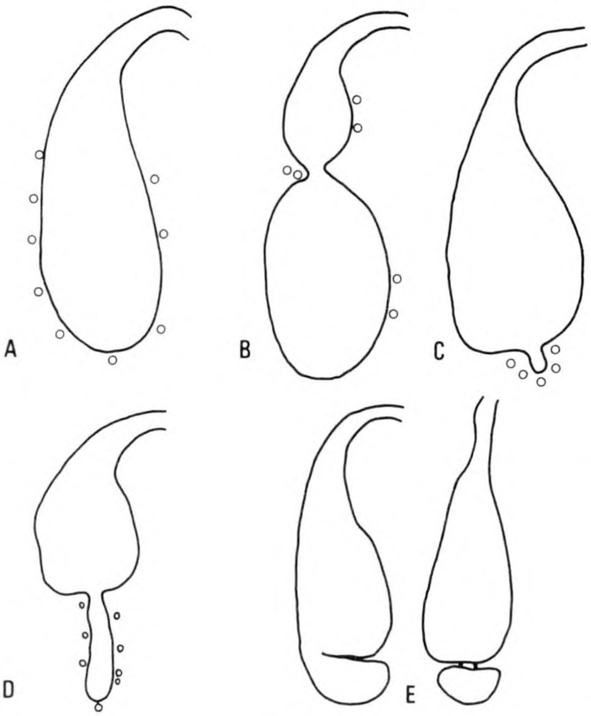

FIG. 2.

Current radiological classification of diverticular disease of the gallbladder. Also, for comparison, the radiological appearance of a Phrygian cap (E). (A) Generalised distribution of diverticula without any stricture. (B) Stricture of the body of the gallbladder. (C) Fundal nodule showing as a small protrusion with a ring of diverticula. (D) An example of a bizarre shaped gallbladder. (E) Two views at right angles of a Phrygian cap anomaly.

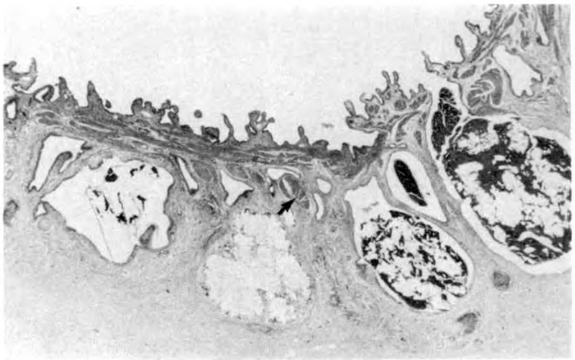

FIG. 3.

Section through the body of the gallbladder in case 13 (Fig. 1). Numerous diverticula are seen outside the muscle layer, and on the right hand edge a connection with the lumen is clearly visible. Most of the diverticula contain bile concretions, but the central sac is full of cholesterol crystals. The muscle layer is thickened, and some fibres are displaced by the diverticula (arrows).

through a thickened muscularis and expanding into cyst-like spaces within the wall (Fig. 3). The diverticula were accompanied by bands of muscle splitting from the main muscularis. There was no distinction from simple Rokitansky–Aschoff sinuses, except in size: the diverticula were more frequent, large and accompanied by wall muscle thickening.

Sections taken in a plane determined by radiography of the operative specimen showed that the fundal nodules were symmetrical about the long axis of the gallbladder. The lumen of each nodule was continuous with that of the gallbladder and surrounded by a rim of thickened muscle penetrated by diverticula (Figs. 4 and 5). There was no increase in mitoses and no evidence of epithelial hyperplasia. The histological appearance of the muscle in the thickened area was the same as that of muscle in the normal wall.

Inflammation was not a major feature in these gallbladders, though minor changes were seen around inspissated bile in the diverticula. The adjacent gallbladder was usually entirely normal with an abrupt change between the lesion and the normal wall. Reparative fibrosis occurred in association with secondary inflammation but it was minor and in no case was the fibrosis sufficient to cause a stricture. There was no evidence of neuromatosis. Cholesterolosis was noted in only one of the fifteen cases. Small biliary concretions were found in many of the diverticula.

Clinical

The fifteen patients with diverticular disease were recalled for interview, but three did not attend. The control group of patients with calculi and no diverticular disease were also interviewed (Table I). No differences were found in the symptoms of the two

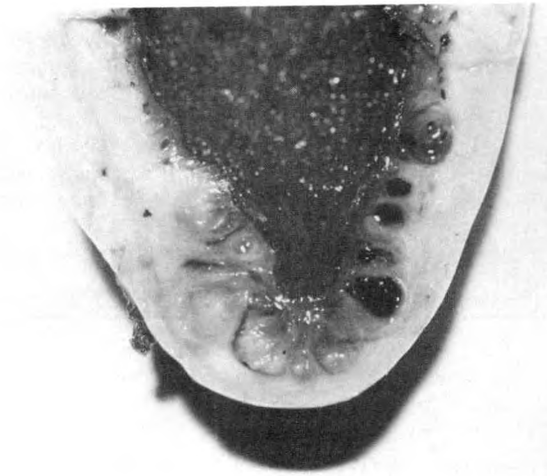

FIG. 4.

Macro photograph of the nodule seen in Case 13 (Fig. 1). Note the stricture near the neck, the numerous diverticula, many containing biliary concretions, and the discrete nodule in the fundus.

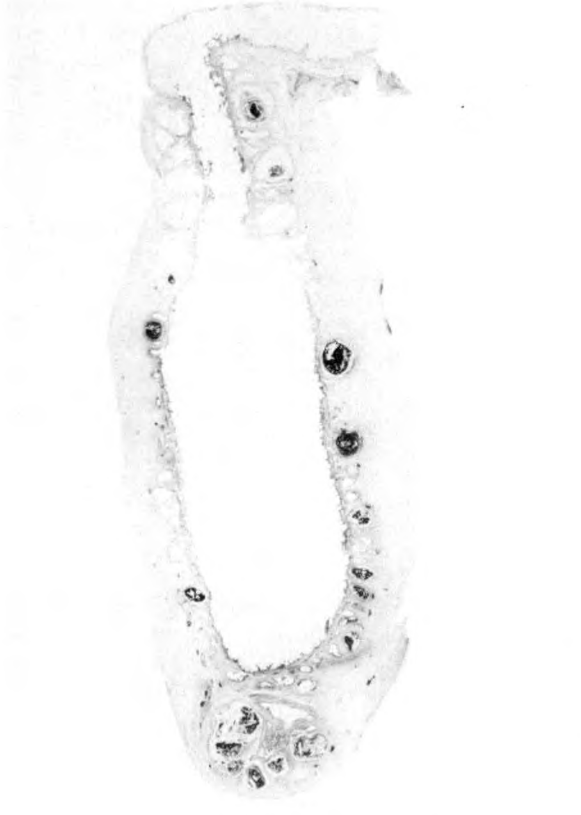

FIG. 5.

Histological section of the whole gallbladder, Case 13 (Fig. 1). Note the stricture near the neck, the numerous diverticula, many containing biliary concretions, and the discrete nodule in the fundus.

groups before operation (Fig. 7). The four patients with acalculous diverticular disease showed no distinctive features. After operation, two patients in each group had symptoms. Heart-burn occurred in one patient in each group, one patient had mild anorexia for ten months after operation. The four patients with acalculous diverticular disease were completely symptom-free and stated that they felt that the operation had been successful.

TABLE I

MATCHED GROUPS OF PATIENTS RECALLED FOR INTERVIEW

	Diverticular disease of the gallbladder	Cholelithiasis only
No. of patients	12	11
No. with stones	9	11
Male : female	3 : 9	2 : 9
Age: range	30–73	27–66
mean	54.2	55.3
Time of interview after operation:		
Range	10–24 months	10–24 months
Mean	16.0 months	15.4 months

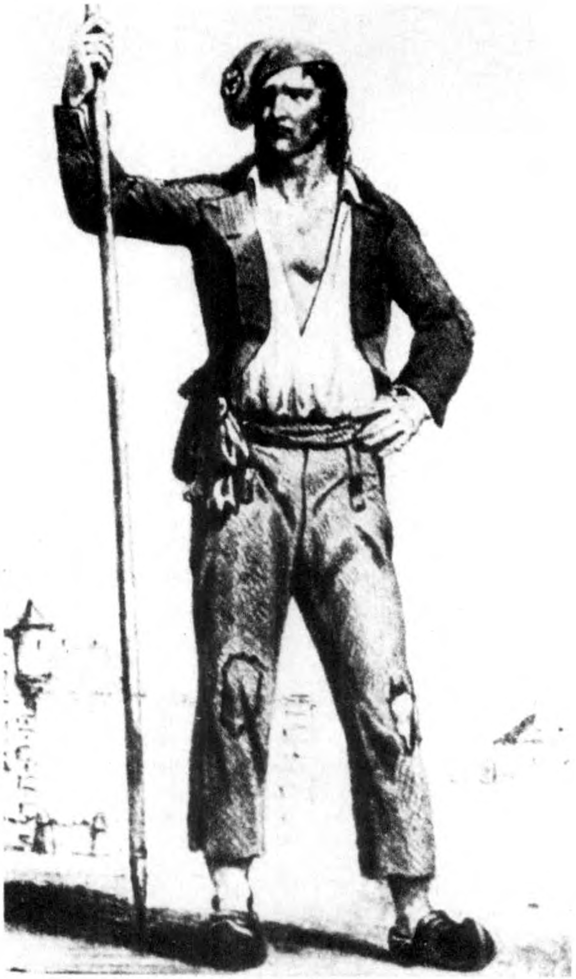

FIG. 6.

A Phrygian cap. Paris fashion at the time of the French Revolution. Older examples show the loculus to have a more pointed shape. (Courtesy ARTIA publishers, Prague)

DISCUSSION

The reported frequency of diverticular disease in surgical specimens varies from 0.8% (Jones & Walker, 1957) to 25% (Goldberg & Dodgson, 1958). It was 21% in the seventy cases presented here.

The primary purpose of this study was to attempt to determine the pathogenesis of the disease using radiological-pathological correlation. Six factors have previously been proposed as playing a role in pathogenesis:

(1) *Neoplasia*

Fundal nodules have been called adenomas or papillomas (Kirklin, 1931), implying a neoplastic process. There was no evidence of neoplasia or of any epithelial dysplasia in our material.

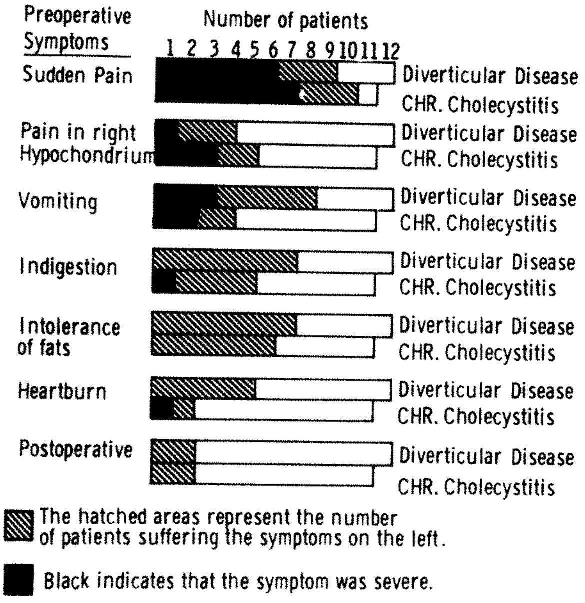

FIG. 7.

Symptoms prior to cholecystectomy in the matched groups of patients recalled for interview. The hatched areas represent the number of patients suffering the symptoms listed on the left; solid areas refer to severe symptoms.

(2) *Inflammation*

This has been alleged to stimulate epithelial growth and to weaken the wall (King & MacCallum, 1931; Goldberg & Dodgson, 1958). There was no evidence of primary inflammatory damage in our series and only minor inflammatory changes around inspissated bile in the diverticula.

(3) *Hypertrophy and hyperplasia*

These have been used to describe the frond-like epithelium and thick muscular wall. No histological justification for these pathological processes was found. There was no reduplication of cell layers and no increase in mitoses in the mucosa and there is no histological evidence to indicate that the protrusions into the wall are anything more than simple diverticula. Boyden's (1925) observations may be relevant. He found that the muscular wall of the contracted cat gallbladder was up to ten times as thick as that of the distended organ and during contraction the mucosa was thrown up into papillary folds.

(4) *Cholesterolosis*

Jutras et al (1960) claimed that their cases of adenomyomatosis were associated with neuromatosis and cholesterolosis, and grouped these diseases under the title of "hyperplastic cholecystoses". No support for such an association was seen in our material.

(5) *Congenital*

Beilby (1967) examined neonatal gallbladders as well as operative specimens. He suggested that all strictures were of congenital origin and that increase in pressure distal to a stricture leads to work hypertrophy of muscle and epithelial pulsion diverticula. This interpretation would seem unlikely. He found no fundal nodules in neonates, and moreover he claimed that the Phrygian cap anomaly was a stricture of the same type as diverticular disease. However, the radiological evidence (Colquhoun, 1961) indicates that a Phrygian cap empties evenly and that its septum does not place a mechanical strain on the distal loculus. Moreover, it has different characteristics radiologically (Figs 2E, 6).

(6) *Muscular dysfunction*

Le Quesne and Ranger (1957) explained the thick muscle as resulting from an unspecified muscular dysfunction. Some direct observations support this suggestion. Samarji (1972), observing contractions in response to pancreozymin at laparotomy, found disturbed contractility in 54 cases of diverticular disease, and the gall-bladder intraluminal pressure was higher than in patients with stones alone. Jutras et al (1960) studied the cholecystograms of patients with diverticular disease and found that contraction was more rapid and more complete than in the normal. Fotopoulos and Crampton (1964), and Jutras et al (1960) showed that the width of strictures may vary from day to day in the same patient, an observation they attributed to "variable spasm". Similar narrowings were observed during excessive contraction of the neck or fundus of otherwise normal gallbladders when stimulated with cholecystokinin or its synthetic analogues (Torsoli et al, 1970; Nathan et al, 1970; Hedner & Anders, 1972). These transient radiological variations in shape resemble those seen in diverticular disease.

Our study supports the suggestion that muscular dysfunction is the basis of the pathological appearances. Histological examination showed no mechanical cause for the narrowing. Similarly there was no evidence of fibrosis or hyperplasia. The narrowing is not simply spasm as it is found in autopsy specimens. It is better explained by a zonal contracture of muscle which impedes full relaxation, as described by Gasser (1930) for striated muscle: this zone having a resting length shorter than normal, contracting and relaxing to a limited extent, but not relaxing fully. Fundal nodules can be explained in similar terms. The shape and symmetrical geometry are compatible with a contracture of the fundal muscle narrowing the lumen, and bunching up the redundant intraluminal mucosa into folds. Penetration of the muscle by the diverticula disrupts the muscular wall, and oblique sections which do not include the central lumen give the histological appearance (Fig. 5) which has generated so many names. Muscular dysfunction would adequately explain why nodules are found only at the fundus. If they were due to hyperplasia they might be expected at any point along the gallbladder wall.

There is marked similarity between diverticular disease of the gallbladder and diverticular disease of the colon, where some muscular dysfunction accompanies diverticula (Williams, 1965). The affected colon has a thick muscle wall with an excess of mucosa in the lumen which is redundant rather than hyperplastic (Morson, 1963). For this reason we suggest that it may be more accurate to call this disease, which has so many names, "diverticular disease of the gallbladder".

The primary purpose of this study was to investigate the underlying pathogenesis, but one important question remains unanswered: Does diverticular disease, in the absence of stones, produce symptoms similar to those of gallstones, and are the symptoms cured by cholecystectomy? This question can only be answered by a larger clinical survey, in order to define the exact clinical significance of diverticular disease. Our experience is similar to that of others, and based on a small number of patients. If the disease is sufficiently advanced to be radiologically recognisable at oral cholecystography, symptoms considered to be due to gallbladder disease will be relieved by removing the gallbladder, with as great a success rate as removing it for stones. It is worth noting that those gallbladders with radiologically visible sacs are very likely to contain biliary concretions in the sacs even if no stones are visible in the lumen. The possible role of these concretions as precursors of calculi could be an interesting future histological investigation.

The clinical significance of this gallbladder abnormality has a contemporary importance to radiologists. At the present time many centres are abandoning the oral cholecystogram in favour of ultrasound (Cooperberg & Burhenne, 1980). The latter procedure is less accurate at detecting diverticular disease than is the oral cholecystogram (de Lacey et al, 1984). It would therefore be wise to consider carefully the roles of oral cholecystography and ultrasound in the diagnosis of gallbladder disease. Furthermore, in such communities the use of films taken after a fatty meal may also require re-evaluation. The main value of the fatty meal is in detecting or confirming diverticular disease, and if abandoned totally it may lead to errors in the diagnosis of this condition (Laufer & Gledhill, 1975; Gajjar et al, 1984).

ACKNOWLEDGMENTS

We thank ARTIA publishers, Prague for permission to reproduce Fig 6. We also thank Kathy Howes for typing.

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A comparison of simplified and standard methods for the measurement of glomerular filtration rate and renal tubular function

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ABSTRACT

Two methods of measuring the clearance of $^{99}Tc^{m}$ DTPA, OIH and iothalamate were compared with standard techniques of measuring the clearance rates of inulin and sodium para-aminohippurate. The best correlation was between the clearance of subcutaneously injected radiolabelled iothalamate or $^{99}Tc^{m}$ DTPA and that of inulin. $^{99}Tc^{m}$ DTPA and ^{131}I OIH clearances measured by a two blood sample technique did not give as good a correlation with inulin and PAH clearances respectively. When measurements of GFR and tubular function were repeated on the same patients the changes measured by inulin and PAH clearances did not correlate with those measured by the two blood sample technique using $^{99}Tc^{m}$ DTPA and OIH. Our results suggest that the clearance of subcutaneously injected iothalamate or DTPA can replace inulin clearance measurements. The two blood sample technique of measuring DTPA and OIH clearance does not directly reflect inulin and PAH clearance and is insufficiently reproducible to be used to follow changes in renal function.

Glomerular filtration rate (GFR) and tubular secretion rate (TSR), measured by the clearance of inulin and of sodium para-aminohippurate (PAH), are two important parameters of renal function, but their use is mainly limited to specialised units because of the cumbersome and time-consuming methods involved. They are however accepted as reference techniques against which simpler methods must be judged. In this study we have compared both of the standard reference methods (Reubi, 1963) with some of the simplified techniques which have been proposed for routine clinical use, namely a two blood sample technique of measuring clearance of radiolabelled ortho-iodohippurate (OIH, Hippuran), $^{99}Tc^{m}$ diethylene triamine penta-acetic acid (DTPA) and ^{125}I sodium iothalamate following single bolus intravenous injection (Smart et al, 1981). We have also compared the standard inulin clearance technique with iothalamate clearance following subcutaneous injection (Israelit et al, 1973).

In one group of patients, GFR and TSR were measured on three successive occasions using the two blood sample technique, with simultaneous measurement of inulin and PAH clearances. The changes in GFR and TSR as measured by the two blood sample methods were compared with changes in inulin and PAH clearances.

METHOD AND PATIENTS

GFR and TSR were measured on 80 occasions in 40 patients between the ages of 41 and 76 (mean 56.8) years admitted for half a day to a "day bed unit" for a comprehensive assessment of renal function, required as part of their clinical work-up for a variety of conditions. None of these patients had oedema or ascites. The tests were conducted with the patients fasting. Renal function ranged from normal to severely compromised. Patients with a history of prostatism or physical signs of urinary retention were excluded. The investigations had previously been approved by ARSAC and by the North Lothian District Ethics of Research Committee.

Three agents were used for the measurement of glomerular filtration rate: inulin, DTPA (Frost) labelled with $^{99}Tc^{m}$, and sodium iothalamate labelled with ^{125}I (Amersham International). The clearances of the three agents were measured simultaneously.

Inulin clearance

After an intravenous bolus injection of inulin (0.4 ml/kg body weight of a 10% solution), a continuous infusion was maintained at a rate calculated for the predicted glomerular filtration rate, over a period of three hours. The patients were encouraged to drink water and were asked to empty their bladder (voluntarily) at the end of each one-hour period. The blood samples were collected at 0 h (before the commencement of infusion), at 1.5 h and at 2.5 h. Inulin clearance was calculated for the two separate one-hour periods (second and third hours).

Iothalamate clearance

0.75 MBq of ^{125}I iothalamate in 0.05 ml was injected subcutaneously into the volar aspect of the forearm at the same time as inulin infusion was commenced. Two blood samples were collected from the other arm at 1.5 and 2.5 h. The iothalamate clearance rates for the second and third hour periods were calculated from plasma and hourly urine radioactivity measurements (Israelit et al, 1973).

Glomerular filtration rate calculated from two blood samples

A bolus of 1 MBq of ^{99}Tc^{m} DTPA in 0.5 ml was administered intravenously at time 0 h. Two blood samples were collected at 60 min and 150 min. The DTPA clearance rate was calculated from these two samples by the method of Smart et al (1981), assuming a mono-exponential clearance of the tracer.

Tubular secretion

A constant infusion of PAH was maintained for the three hours following a bolus intravenous injection. Its clearance was calculated for the second and third hour periods as described for inulin clearance.

Measurement of OIH clearance by a two blood sample technique

A bolus of 2 MBq of ^{131}I OIH in 2.5 ml was injected intravenously at 0 h. Two blood samples were collected at 60 and 150 min. Clearance was calculated assuming mono-exponential excretion of the tracer by the kidneys (Smart et al, 1981).

All the injections were given at time 0, after control blood and urine samples had been collected. Three venepunctures at 1 h, 1.5 h and 2.5 h were made from the other arm for the collection of blood samples. Samples from the second and third hour urine collections were used for aminohippurate, inulin and iothalamate assay. No estimate was made of residual bladder volumes. The blood and urine sample radioactivity was measured using a Wallac 8000 gamma sample counter, on the same day and three days after the collection, to allow the ^{125}I to be counted after decay of ^{99}Tc^{m}. The first count was made using window settings for ^{131}I and ^{99}Tc^{m} and the second for ^{131}I and ^{125}I. Inulin and PAH were measured spectroscopically using a Technicon autoanalyser (Dawborn, 1965).

In seven patients GFR and TSR were measured by the two blood sample technique on three separate occasions, six weeks apart. The difference between results obtained on separate occasions in the same patient was compared with the difference between simultaneously measured inulin and PAH clearances. The methods employed are described above.

On 16 occasions intravenous ^{125}I iothalamate was used for the two blood sample measurement of GFR and the ^{99}Tc^{m} DTPA given subcutaneously The procedure was otherwise as described above.

Statistical methods

Correlation coefficients were calculated for the clearances compared with inulin and PAH The slope of the regression line and variance of y about the regression line was calculated. The 95% confidence interval for the estimate of the true slope as well as the 95% confidence interval for an individual value of y at any value of x are shown in Figs. 1, 2 and 3 by solid and dashed lines respectively.

Results

Three groups of tests were carried out:

(a) A direct comparison of the different methods of measuring GFR and TSR;
(b) A comparison of the results of repeated measurements in the same patient on three occasions;
(c) A cross-over of ^{99}Tc^{m} DTPA with ^{125}I iothalamate.

Inulin clearance and clearance of subcutaneously injected iothalamate were compared in 76 one-hour periods out of the total of 80 measurements (two for each patient) The omissions were due to technical problems and difficulties with infusions. The calculated glomerular filtration rates ranged from 7 ml/min to 182 ml/min. The correlation coefficient for the two methods is 0.86, the variance of y about the regression line is 484 (SE = 2.5) and the slope 0.8. The line of best fit and 95% confidence intervals are presented in Fig. 1.

Inulin clearance was also compared with the two blood sample technique of glomerular filtration rate measurement. Thirty-seven DTPA clearances (measured over 2.5 h) were compared with the corresponding inulin clearances during the two hours following the injections. The correlation coefficient was 0.77 with a variance of 1044 (SE = 5.3) (Fig 2). The slope of the line of best fit is 0.94.

The clearance of ^{131}I OIH measured by the two blood sample technique was compared with PAH clearance performed at the same time. The calculated correlation coefficient for the 46 measurements was 0.65 with a wide scatter of y about the regression line (SE = 32.8), the slope for the line of best fit being 0.81 (Fig. 3).

The urine volumes were compared with the difference

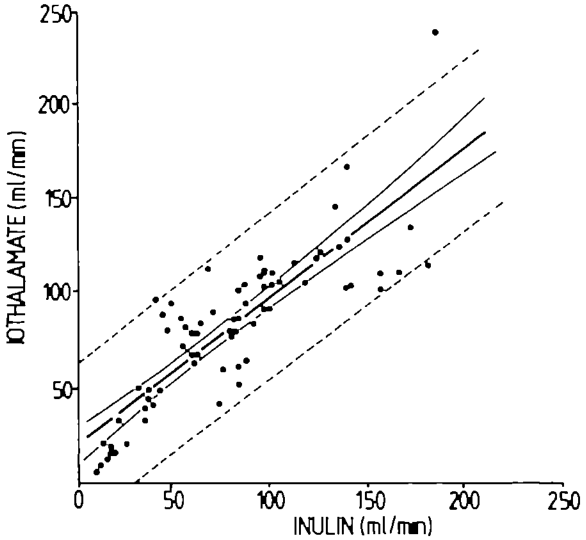

Fig. 1

Subcutaneously injected iothalamate clearance as compared with inulin clearance ($n = 76$, $r = 0.86$, $y = 19.5+0.80x$).

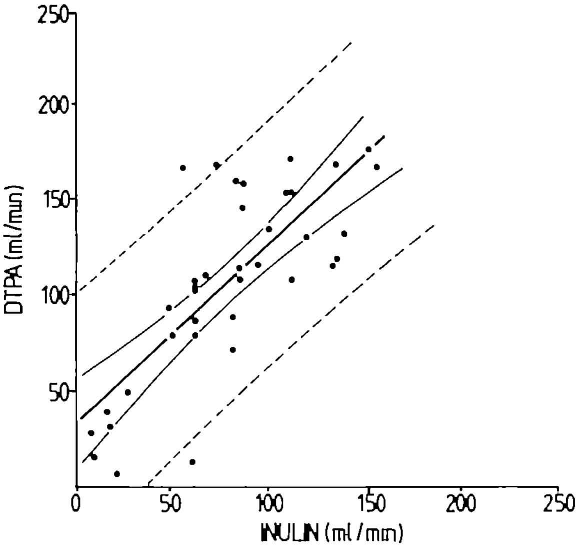

FIG. 2.

Intravenous DTPA clearance as measured by two blood sampling method compared to inulin clearance ($n = 37$, $r = 0.77$, $y = 33.7 + 0.94$)

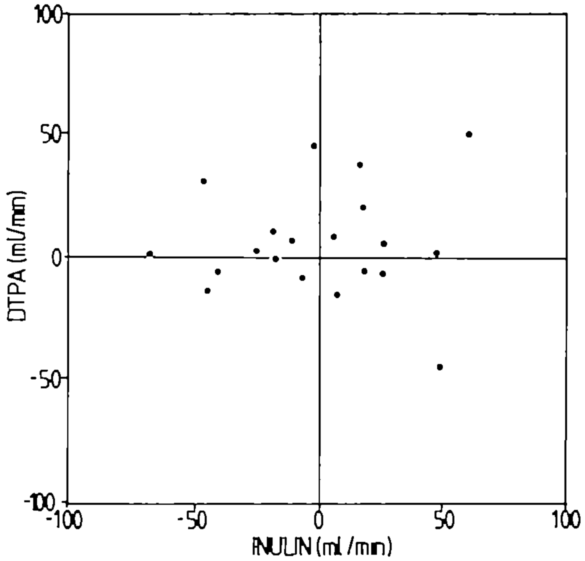

FIG 4.

Comparison of changes in DTPA clearance and simultaneously measured inulin clearance in the same patients on successive measurements ($n = 20$, $r = 0.04$)

of clearances between the methods requiring urine samples and the methods not requiring urine collection. If the difference was due to errors in collection, then one would expect bigger differences for smaller urine volumes. There was no correlation between these parameters ($r = -0.083$) with urine outputs ranging from 30 to 570 ml per hour.

On 16 occasions the isotopes used in GFR estimation were exchanged, ^{99}Tc^{m} DTPA being given subcutaneously and ^{125}I iothalamate by intravenous bolus. The correlation coefficient, comparing with inulin clearance, was 0.69 for the two blood sample method and 0.85 for the subcutaneous method, which is not significantly

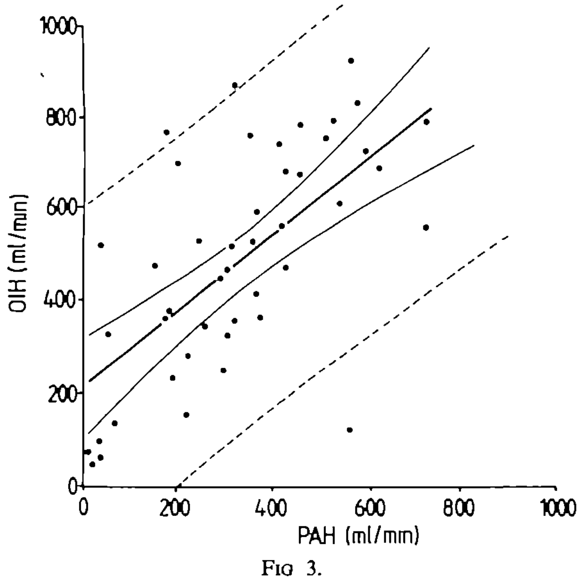

FIG 3.

Intravenous OIH clearance as measured by two blood sampling method compared to PAH clearance ($n = 46$, $r = 0.65$, $y = 218 + 0.83x$).

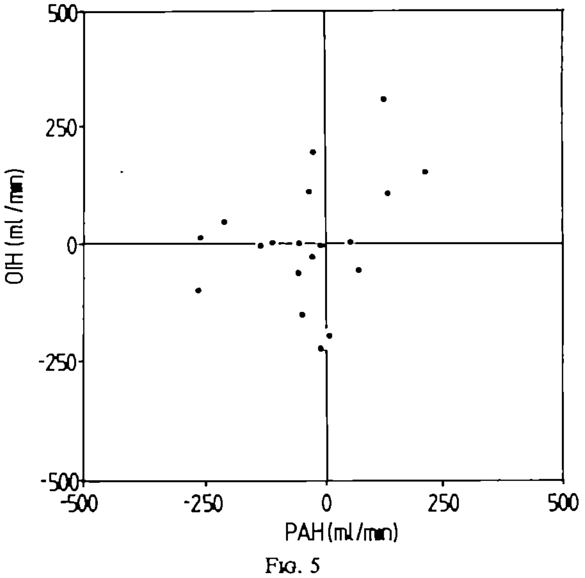

FIG. 5

Comparison of changes in OIH clearance and simultaneously measured PAH clearance in the same patients on successive measurements ($n = 20$, $r = 0.32$)

different from the previous measurements (before the cross-over).

Clearances were measured on three occasions in seven patients. Changes in inulin clearance were compared with those of ^{99}Tc^{m} DTPA clearance by the two blood sample technique. The differences in inulin clearance were in the range of 1.5 to 67.5 ml/min (mean of 31.3) There was no correlation between the changes as measured by the two methods (r = 0.04, Fig. 4). A similar lack of correlation was found between the changes measured in PAH clearance (range 2.5 to 258.5 ml/min, mean 115.2 ml/min) and those measured by the two blood sample technique with ^{131}I OIH (r=0.32, Fig. 5).

DISCUSSION

Inulin clearance was proposed as a means of measuring glomerular filtration rate in 1935 by Shannon and Smith and also by Richards et al (1934). This method is well established and has been accepted as a standard against which other methods are evaluated. Continuous search for new and simpler methods, as well as limited use in daily clinical practice, highlights the difficulties with this method.

The disadvantages of inulin and PAH clearance methods are:

1. Continuous intravenous infusion at a constant rate is required. This can be difficult to manage, even with modern infusion pumps.
2. The validity of the measurements depends largely on the accuracy of the urine collections. If performed over a short period of time (10 minutes or so) urethral catheterisation of the patient with bladder washouts is required, with its inherent risks and discomfort to the patient.
3. All the procedures require constant supervision. This is time-consuming for the patient and the technician involved

As a general rule, the more time-consuming and difficult a procedure, the more limited is its use in daily clinical practice We have relied on voluntarily voided urine collections, and to minimise the errors we have extended the 10-minute period (with bladder washouts) to a one-hour period (with no bladder catheterisation), during which patients passed an average of 247 ml of urine

Constant infusion of PAH and inulin is essential for measurement of their clearances. Subcutaneous injection of a small volume of iothalamate or of ^{99}Tc^{m} DTPA gives predictable blood levels, thus eliminating the need for infusion. The concentration of radioactivity in plasma falls by one half over the 150 minutes of the study, in a linear fashion. This method of glomerular filtration rate measurement, which still requires hourly urine collections, gives a good correlation with inulin, there being no major difference in clearance rates over a large range of renal function irrespective of whether iothalamate or ^{99}Tc^{m} DTPA is administered. One subcutaneous injection, one period of urine collection and one blood sample makes such a test feasible within the half-day of a clinic visit. Several patients can be supervised at the same time. Because of the good correlation with inulin, the acceptably small standard error and its simplicity, we consider this the best of the methods compared, despite the need for urine collection.

Because, in the present study, the same urine samples were used both for the inulin and the radioisotope assay, any errors due to incomplete voiding cancel out. Radiation counting statistics account for less than 1% of the observed error. A principal source of error in the comparison is probably the inulin assay. Although it is nominally relatively accurate, blind duplicate assays on separate aliquots from the same sample suggested that the reproducibility may be poorer than was thought. Confidence limits for the prediction of inulin clearance from that of subcutaneous iothalamate or DTPA are fairly wide, indicating that the smallest detectable real change between two individual readings is substantially larger than is sometimes implied.

In a preliminary trial subcutaneous injection proved to be unsuitable for measurement of ^{131}I OIH clearance because it did not give a stable blood level over a useful subsequent period. PAH clearance was therefore only compared with OIH clearance calculated by the two blood sample technique.

Rigorous techniques using the bolus injection of filtered or excreted substances without urine collection require multiple venous blood samples, very accurately timed (Ladegaard-Pedersen, 1972) or external counting (Blaufox et al, 1967) to define the blood clearance curve, which is not mono-exponential. These are uncomfortable for the patient and are time-consuming. Estimation of GFR and tubular function by simplified techniques has attracted much attention (Blaufox & Merrill, 1966; Tauxe et al, 1975; Mackay et al, 1981; Brochner-Mortensen & Freund, 1981). In this study we have compared one widely used method, which requires two blood samples and assumes a mono-exponential clearance, with inulin and PAH clearances. The results were not as satisfactory as published results suggest. OIH clearance estimated by this method resulted in higher figures for clearance rates than PAH even though OIH clearance is said to be lower than that of PAH (Maher & Tauxe, 1969). The correlation coefficient of 0.65 is lower than with either of the techniques employing filtered agents and there is a wide scatter about the regression line. The 95% confidence interval for individual OIH clearance values at any given PAH clearance encompasses a range of about 650 ml/min (Fig 3). This level of uncertainty for individual measurements is unacceptable for clinical purposes

As a measure of GFR the two blood sample method of estimating DTPA clearance correlated almost as well with inulin clearance (r=0.77, intercept 32.3, slope 0.94) as the subcutaneous method. The scatter about the line of identity is however greater than with the subcutaneous technique and the confidence limits for the prediction of the value of x for any given value of y substantially wider, although not as wide as the PAH/OIH comparison. A number of factors contribute to this, including the random errors inherent in collection of voluntarily voided urine. However the lack of correlation between scatter and the volume of urine excreted suggests that this is not the principal source. Other factors such as the errors inherent in assuming a single exponential, fitting it using only two points, and variations in radiopharmaceutical purity of the DTPA (Russell et al, 1983) must play a major part. Even though the DTPA was freshly prepared for each patient and the labelling efficiency of the preparation was normally better than 95%, unrecognised variations in individual samples could not be excluded. A preparation with a long shelf-life such as iothalamate eliminates this latter problem but does not reduce the scatter. Some DTPA kits which have become available since this study was completed have a higher and more reproducible labelling efficiency than the kits used. Overall the evidence suggests that the critical limitation of this approach is the cumulative crudity of the mathematical approximations involved.

A crucial requirement when assessing a renal function test is its ability to detect small changes in function, such as are induced by drugs, diet and other physiological and pathological conditions, by repeated measurements on the same patient. Reproducibility is thus crucial. In the seven patients who required renal function measurements on three occasions, the changes determined by inulin and PAH clearances were compared with those of simultaneously measured DTPA and OIH clearances. No correlation was found, indicating that the changes measured by inulin and PAH methods were not reflected in changes measured by the two blood sample technique. The reason is evident from Figs. 1 and 2 and the preceding discussion. Thus although the confidence limits for the lines of identity are suitably narrow, indicating that the two parameters are related, the confidence limits for the calculation of the value of x for any given value of y are wide because of the cumulative effect of all of the errors in each measurement. The smallest real change in function that can be detected is in consequence very large.

Thus our results indicate that accurate and reproducible measurements of GFR require either urine collections, the accurate delineation of the blood clearance curve, or both. These measurements can be combined with gamma camera renography, using either multiple blood samples or the heart or some other suitable non-renal area to define the blood clearance curve, increasing the information obtained but at the cost of prolonging the examination.

We have not been able to determine the extent to which physiological variation accounts for the observed scatter, but that found when two different methods are performed simultaneously suggests that errors inherent in the techniques employed are the major limitation on accuracy. In view of the simplicity and precision of measurements of blood urea and of creatinine clearance, any method employing radioactive tracers must be shown to possess a clinically significant advantage before being advocated for routine use. We believe that existing methods are too imprecise to fulfil this recognised clinical need.

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Book reviews

Head and Spine Imaging. By C. F. Gazalez, C B. Grossman and J C. Masden, pp 952, 1985 (John Wiley & Sons, New York), £181 35.
ISBN 0471–89747–7

This is a substantial multiauthor text, with contributions from diagnostic radiologists, radiotherapists, clinicians and physicists, all but one of whom are drawn from the USA. The editors reflect this interdisciplinary approach and, as well as their overall direction of the work, they have personally contributed several chapters.

The introductory sections deal with the basic principles of currently available imaging techniques applicable to the brain, embracing CT, NMR, neurosonography and positron emission tomography (PET). The chapters on CT are particularly detailed and cover developments in CT design, radiation dose, image quality and analysis, artefacts, reconstruction techniques and performance limits. The different scanning techniques (conventional transaxial, direct sagittal and coronal, target scanning, rapid sequence and contrast enhancement, *etc.*) and their clinical applications are also considered in depth There is also a useful short account of the various factors which need to be considered in the selection of a CT scanner and the design of a CT scanning suite All this provides much useful and practical information, especially for radiologists about to embark on CT scanning

The development of reliable, portable, real-time ultrasound equipment has made neurosonography of the infant brain, and the application of the technique as an intra-operative procedure, a reality This technique and the general use of neurosonography in the infant are described in detail and compared with CT.

The normal anatomy of the brain is described in considerable detail with the aid of line diagrams, pathological sections matched to comparable MR images, and contrast enhanced CT sections Although some of the annotated sections are rather "busy", the various anatomical structures illustrated are easy to identify The more clinically orientated sections cover all forms of cerebral pathology (neoplasms, vascular disorders, trauma, infections and inflammatory disease, hydrocephalus and atrophy). The same is described for children, which leads inevitably to a certain amount of repetition The application of CT to radiotherapy planning is also described Separate chapters are devoted to specific regions such as the orbit, sella and suprasellar areas, the skull base, sinuses, and temporal bones. In each of these chapters the authors share their expertise with the reader and outline the optimum scanning technique applicable, for example high-resolution (1.5 mm) target scanning with extended scale for the demonstration of petrous anatomy. The book concludes with post-operative complications and the application of CT and, briefly, MR to the examination of the spine The CT images are generally of extremely high quality, where possible these have been obtained on third or fourth generation scanners. The MR images are not of the resolution and quality now obtainable, but this is inevitable in a field where technological developments are occurring so rapidly

The main emphasis of the work is on CT, for which the authors make no apology They maintain correctly that CT has "come of age", and base this on the abundance of clinical studies and clinico-pathological correlations compiled over the last 10 years or more. Few would take issue with their view that, despite the introduction of NMR, CT will remain an important imaging technique in the neuro-sciences for some considerable time yet

The text is well organised and lucid, with a good reference index. Comprehensive lists of references, some in excess of 100, are given at the end of each chapter, and generally cover the period 1970 to 1983

This book is well written, well produced, and contains a wealth of information It would serve as an invaluable reference text in any neuroradiological department, and would be well worth the considerable financial outlay necessary for its purchase This could well become a standard work on the topic.

J E ADAMS

A Handbook of Radioactivity Measurements and Procedures. NCRP Report No 58 2nd Edition, pp. xvi + 592, 1985 (NCRP Publications, Washington D C), $25 00
ISBN 0–913392–71–5

The first edition of this book was reviewed in the journal in 1979 (*Vol 52,* p. 919) by G. R. Newbury. The review, which was very complimentary, describes its development from *The National Bureau of Standards USA Handbook 80* and outlines the topics covered by the book. One surprising aspect of that review was the suggestion that it would rarely be of value to clinicians or biologists Certainly it is a must for most physicists working in this field, but many biologists have resorted to its pages for a better understanding of the radiation-measurement techniques involved in the production of their results.

This second edition reflects the success of the first; any changes are by expansion and addition. The first two sections of the handbook on the more basic considerations have only a small addition characterising performance of semiconductor detectors Additions have been made in the third section on experimental measurement techniques of complex β–γ decay in β–γ coincidence-counting, and on liquid-scintillation counting in both the third and fourth sections. Sections five, six and seven are little changed from the first edition and are more concerned with application and interpretation of measuring techniques which can be especially useful in fields where radioactive assay is seen only as a step towards an end in an unrelated field A major and valuable addition, "Measurements Assurance, Standards, Tracibility and the Statement of Uncertainty", has been made to the eighth section which, though of more use in the USA, has a relevance elsewhere

The nuclear-decay data tables have been revised to include the latest information from the Oak Ridge data banks and form a large and useful appendix to the book. The mean energy emitted per time integral of activity for each nuclide is given, as in the first edition, and this is of particular relevance to medical, biological, and health-physics applications

This second edition is best seen as a worthwhile updating of a good standard textbook on the subject of radioactive measurements in many fields and is well worth its cost

T E F CARR

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Delayed reactions to urographic contrast media

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ABSTRACT

Reactions to urographic contrast media occurring after the patient had left the department were studied by giving patients a questionnaire to complete. 841 questionnaires were returned (about 80% of those issued). 70% of patients had no delayed reactions and 7% expressed a positive response to urography *i.e.*, found the procedure interesting and not unpleasant; 13% had arm pain, 5% a rash and 14% had a variety of reactions, many of which were the same as those described in iodism.

Women had significantly more rashes (7%) than men (4%) and those media containing the meglumine or iodamide ions caused more rashes than other media.

Conray 420 caused more arm pain than Conray 280 or the non-ionic media, which would be expected from the known effects on vascular endothelium.

Symptoms of iodism were equally common from the various contrast media.

During the course of a large survey of reactions to urographic contrast media carried out in the United Bristol Hospitals from 1968 to 1970 (Davies et al, 1975) one of the present authors observed that some patients had had delayed rashes after previous urography. In two cases these recurred after the current urogram with exactly the same clinical features. Other patients had a 'flu-like illness on the evening of urography. The occurrence of delayed phlebitis is common knowledge.

The introduction of non-ionic agents suitable (if expensive) for urography prompted the setting up of a trial to compare various contrast media and as part of the trial it was decided to investigate delayed reactions by means of a questionnaire.

PATIENTS, MATERIALS AND METHODS

All patients aged between 18 and 70 years, with no known renal disease or impairment, and who were referred for non-emergency urography over a nine-month period were included in the study. Seven different agents were used, viz. sodium iothalamate (Conray 420), meglumine iothalamate (Conray 280), sodium/meglumine diatrizoate (Urografin 370), sodium iodamide (Uromiro 300), iopamidol (Niopam 370) and two strengths of iohexol (Omnipaque 240 and Omnipaque 350). In no case was it considered necessary to select a particular agent on the basis of previous reaction to contrast examinations.

Urography was performed using 50 ml of the selected medium. Patients who received a second injection were excluded from the present study.

Immediate reactions have been reported elsewhere (Davies et al, 1985).

Each patient was given a letter with a questionnaire and asked to return the questionnaire, using a postage-paid envelope, at least one week after the examination. The following questions were asked:

- — Did you have pain in the arm after the examination?
- — If so, was it where the injection was made?
  was it above this site?
- — How many days after the examination did it come on?
- — How many days did it last?
- — Did you have a rash after the examination?
- — If so, could you give brief details
- — Do you have any other comments?

The returned forms were analysed manually.

RESULTS

841 questionnaires were returned (78% of those issued) of which 485 were from men and 356 from women (79% and 76% respectively).

Nine per cent of the men and 5% of women expressed positive comments about the examination, either thanking the staff, stating that they had found the warm feeling not unpleasant, or commending the carrying out of the trial. Altogether 70% had no adverse delayed reactions.

The returned forms provided two types of data—(i) replies to specific questions, and (ii) free text comments.

Tables I (Type (i) data) and II (Type (ii) data) summarise the incidence of the most frequently reported reactions.

TABLE I

REACTIONS REPORTED BY PATIENTS AS OCCURRING AFTER THEY HAD LEFT THE DEPARTMENT (TYPE (i) DATA)

	Male (%)	Female (%)	Total (%)
Total cases	485	356	841
No reaction	363(75)	227(64)	590(70)
Delayed arm pain			
— At injection site	20(4)	36(10)	56(7)
— Above injection site	28(6)	45(13)	73(9)
— Unspecified site	2(0.4)	3(1)	5(0.5)
— Total*	46(9)	66(19)	112(13)
Delayed rash	17(4)	26(7)	43(5)

*Some patients experienced pain at more than one site

TABLE II

REACTIONS REPORTED BY PATIENTS AS OCCURRING AFTER THEY HAD LEFT THE DEPARTMENT (TYPE (ii) DATA)

Reaction	Total no.
Headache	24
Tired, weak, etc.	40
Felt ill, unwell (symptoms not specified)	23
Dizzy	9
Vomiting	8
Nausea	6
Taste disturbance	5
Diarrhoea	4
Stomach ache/pain	10
Aching joints	6
Upper respiratory symptoms	10

Delayed rashes (Type (i) data)

Delayed rashes were reported by 43 patients (5%) The onset was within 3 days and the duration up to 8 days The most commonly described lesions were "red blotches", "red raised lumps", and "heat lumps", and itching was a prominent feature. One patient described a scaly rash on his forehead, and another dry skin with blisters around the nose which lasted several days.

The incidence of rashes with each agent was compared (Table III). Women had more rashes than men ($0.05 > p > 0.02$). Altogether 7% of the women and 4% of the men reported delayed rashes. There was no significant difference between Conray 420 (6 rashes in 230 cases) and the non-ionics (7 rashes in 214 cases). There was a significant difference between Urografin 370, Conray 280 and Uromiro 300 as one group and Conray 420, Niopam and Omnipaque as the other ($0.01 > p > 0.001$).

Arm pain (Type (i) data)

Delayed arm pain was reported by 112 patients altogether (13%) of whom 73 (9%) stated the pain was above the site of injection. The onset of pain ranged from 0 to 8 days (mean 1.6 days). The duration of pain ranged from 1 to 30 days (mean 3.4 days). In 82 cases, the pain lasted two days or more. Ten patients commented that the pain was severe, and three reported that a diagnosis of phlebitis had been made by their GP, and treatment given.

Women had a significantly higher incidence of delayed arm pain than men. The incidence of delayed arm pain with each agent was compared (Table IV).

The incidence following the use of Conray 420 was significantly greater than that following Conray 280 ($0.02 > p > 0.01$) or non-ionic agents ($0.01 > p > 0.001$). There was no significant difference between Conray 420 and Urografin ($0.5 > p > 0.1$) nor between Conray 420 and Uromiro

TABLE III

INCIDENCE OF RASHES

Agent	No of cases	No. of rashes (%)
Conray 420	230	6(3)
Conray 280	188	14(7)
Urografin 370	119	9(8)
Uromiro 300	90	7(8)
Niopam 370	69	3(4)
Omnipaque 240	69	1(1)
Omnipaque 350	76	3(4)
Total	841	43(5)

Other delayed reactions (Type (ii) data)

Many other reactions were reported. The most common are listed in Table II: others were itching (3), sweating or fever (3), loss of appetite (3), constipation (2), depression (1), swelling of testicle (2), vaginal irritation (1), loss of libido (1), ankle swelling (1)

Eight patients reported feeling sick and generally unwell for between three and seven days, three with vomiting.

Three further patients reported severe vomiting which was delayed for three, five and ten hours respectively.

Two patients suffered asthma attacks, one of which lasted for three days in a patient who had not suffered with asthma for 38 years, the other coming on three days after the injection, although the asthmatic status of the patient was not known.

An interesting effect was reported by two patients who said that their previously cold feet had not been cold since the examination (Omnipaque 240 and Conray 420 respectively).

Iodism

Patients reporting loss of appetite, sickness, headache, abdominal pain, constipation, diarrhoea, 'flu-like symptoms, extreme tiredness, depression or taste disturbance were grouped together as these are all

TABLE IV

INCIDENCE OF ARM PAIN

	Delayed arm pain above injection site No. (%)	Delayed arm pain—all sites No (%)
Conray 420	35(15)	45(20)
Conray 280	13(7)	21(11)
Urografin 370	11(9)	16(13)
Uromiro 300	10(11)	14(16)
Niopam 370	3(4)	7(10)
Omnipaque 240	0(0)	3(4)
Omnipaque 350	1(1)	6(8)
Total	73(9)	112(13)

TABLE V

PATIENTS SUFFERING FROM SYMPTOMS OF IODISM

	Cases (men)	Reaction no (%)	Cases (women)	Reaction no. (%)	Cases (total)	Reaction no (%)
Conray 280	1034	6(6)	85	12(14)	188	18(10)
Conray 420	137	10(7)	93	11(12)	230	21(9)
Uromiro 300	52	2(4)	38	4(11)	90	6(7)
Urografin 370	69	6(9)	50	2(4)	119	8(7)
Niopam 370	40	4(10)	29	4(14)	69	8(12)
Omnipaque 240	41	2(5)	28	4(14)	69	6(9)
Omnipaque 350	43	3(7)	33	5(15)	76	8(11)
Total	485	33(7)	356	42(12)	841	75(9)

recognised symptoms of iodism. The results for the seven contrast agents are laid out in Table V.

None of the differences is statistically significant and in particular there is no evidence of any relation to dose.

DISCUSSION

Reports in the literature of delayed reactions are infrequent and usually anecdotal. This paper reports the first attempt to study delayed reactions in a formal manner. We think the response rate of about 80% with a level of reactions of 31% indicates that any bias in reporting reactions is small.

Rashes

Ansell et al (1980) have suggested that delayed rashes may be more common than is realised, and a number of cases have been reported (Ansell, 1968, 1970; Heydenreich & Larsen, 1977; Good et al, 1980).

Delayed rashes were reported by 5% of patients in the present study. About 1% of patients have been shown to develop immediate rashes (Davies et al, 1975) Urografin 370, Conray 280 (both containing the meglumine ion) and Uromiro Sodium 300 formed one statistical group, with more rashes than Conray 420 and the two non-ionics. Thus the iothalamate ion is responsible for the same number of delayed rashes as the non-ionics, and presumably the sodium ion has no effect on this. The increased number for Conray 280 and Urografin 370 can be attributed to the meglumine ion Presumably the iodamide ion produces more delayed rashes than the iothalamate ion.

Delayed arm pain

Arm pain during the injection of contrast agents has been shown to result from clinically inapparent perivenous injections and venous spasm (Davies et al, 1975) Delayed pain, particularly some distance from the site of injection, is likely to be due to a direct toxic effect on the endothelium with thrombophlebitis. This effect has been demonstrated experimentally, and shown to increase with the osmolality and sodium concentration of the contrast medium (Mersereau & Robertson, 1961; Penry & Livingston, 1972).

Thrombophlebitis has long been recognised as a complication of lower limb phlebography, with incidences of up to 32% being reported, and it has been suggested that this might occur in the arm following urography (Bettmann & Paulin, 1977).

The present study shows that delayed arm pain is in fact very common, with an incidence of up to 14%.

Presumably, the majority of cases resolve without treatment and probably constitute little more than a nuisance to the patient. However, it is clearly an undesirable side effect of urography, resulting in some patients in severe pain and disability.

Our present results indicate an increase in the incidence of arm pain following the use of agents containing sodium salts (Conray 420, Urografin 370 and Uromiro), there being no significant difference between these agents, thus supporting Penry's experimental findings. There was a greater incidence of arm pain from ionic than non-ionic agents which supports the findings of Lea Thomas that non-ionic contrast media cause less endothelial damage (Lea Thomas et al, 1984).

Iodine toxicity (iodism)

Iodism is a syndrome caused by iodine or any iodine compound, which includes the following amongst recognised symptoms: unpleasant brassy taste; soreness of teeth and gums; coryza, sneezing and irritation of the eyes, "head cold"; severe headache; productive cough; inflammation of the salivary glands, pharynx, larynx and tonsils; skin lesions of varying types (see above); gastric irritation and diarrhoea. Fever is occasionally observed and patients may develop anorexia and depression (Goodman & Gilman, 1980).

Harris et al (1970) stated that high doses of inorganic iodides taken for extended periods will provoke chronic iodide poisoning, but that symptoms of iodism were not conspicuous following urography. However, one of its more dramatic, if infrequent manifestations—that of acute parotitis or "iodide mumps"—has been reported on a number of occasions following urography (Koch et al, 1969; Kohri et al, 1977; Navani et al, 1972; Sussman & Miller, 1956; Talner et al, 1971).

Seventy-five patients in our present study (9%) reported symptoms which could be attributed to iodism, and which lasted more than one day, and several patients reported quite severe constitutional upsets lasting for several days.

That there was no significant difference in the incidence of iodism between the media is not surprising, since iodism is known not to be dose-dependent and to represent, at least in part, an idiosyncratic reaction. Iodism is significantly more common than delayed rashes and is a more important side effect of urographic agents.

Conclusions

(1) Delayed reactions after urography are relatively common; about 30% of patients suffer from them.

(2) Delayed rashes (5%) are more common than immediate rashes (1%).

(3) Arm pain is less common after the administration of non-ionic media than of sodium-containing ionic media.

(4) The incidence of "iodism" is the same for non-ionic and ionic media (9%) and is nearly twice the incidence of delayed rashes.

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The long-term hazards of the treatment of thyroid cancer with radioiodine

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ABSTRACT

Two-hundred and fifty-eight patients treated with high-activity ^{131}I for thyroid cancer and on prolonged follow-up have been reviewed to determine long-term hazards and their relation to the radiation dose received. The expectation of life of those dying from causes other than cancer was slightly reduced in the female patients. A small, significant excess of deaths from cancer of the bladder and from leukaemia was found which, assuming that these were due to radiation, gave inferred risk-rates respectively of 0.4 and 4.9 deaths per 10^4 PYG (patient-year-grays) to the bladder wall and red marrow. Of 31 younger patients (eight male, 23 female), four of the marriages have been infertile. The fertile marriages produced a total of 44 live births Considerable gonad irradiation (estimated 0.8–2.7 Gy) was compatible with apparently normal fertility Despite the high level of irradiation of the salivary glands, no malignancies and only one adenoma was found. Impaired pulmonary function occurred in only one of the patients who had diffuse bilateral metastases. In this patient, tumour in the lung was persistent throughout, so that radiation was probably not alone responsible.

Radioactive iodine (^{131}I) has now been used for nearly 40 years for the treatment of hyperthyroidism and thyroid cancer. The carcinogenic hazard in relation to the treatment of hyperthyroidism has been examined in several follow-up studies; a recent one by Hoffman and his associates (1982) showed no excess of breast cancer or leukaemia but a suggestive excess of cancer in organs that concentrate ^{131}I (salivary glands, digestive tract, kidney and bladder). Although several follow-up studies of patients treated with ^{131}I for thyroid cancer have been published, these have been directed towards therapeutic effects rather than towards side-effects (Leeper, 1973; Tubiana et al, 1975; Maheshwari et al, 1981; Brown et al, 1984). Little information is available therefore about the long-term hazards of ^{131}I treatment of thyroid cancer although this involves the administration of much larger activities than are used for the treatment of hyperthyroidism. Pochin (1969) reviewed one group of patients treated for thyroid carcinoma and in the present work we update this review to 15 years when more patients have been treated and followed for a considerably longer period. The observations are related to the estimated organ irradiation

METHODS

Patients

Between 1949, when the first patient was treated and January 1983, 365 patients were treated in the clinic at University College Hospital. The treatment schedule of an initial ablation by ^{131}I, usually with 2.9 GBq (80 mCi), followed, when necessary, by further treatment with one or more 5.5 GBq (150 mCi) amounts at intervals of a few months, has remained little changed during this period and is described in detail elsewhere (Pochin, 1971, Edmonds, 1979). We have chosen to limit this study to patients who have been followed up for at least two years after commencing treatment.

One-hundred and seven patients were thereby excluded, of whom 86 died of rapidly progressive thyroid cancer and three died from cardiovascular disease or infection. We have inadequate follow-up on 18 of these patients, of whom 12 were non-UK residents and did not attend follow-up and a further six have proved untraceable. The present results are based on the remaining 258 patients (Fig. 1) who had been followed-up for at least two years at the date of the review (1 January, 1983). The follow-up has been complete in 241 (93%) of these patients. In the remaining 17 patients, follow-up averaged 9±4.1 years but has not been complete because they were not resident in the UK or they had emigrated, or were untraceable. The patients were ordinarily seen at 6–12 monthly intervals when on long-term follow-up so that the appearance of any intercurrent condition could be reliably recorded. The mean follow-up period in the 241 patients was 11.2 years, and of the years at risk 78% were derived from patients followed up for 10 years or more; 59% derived from patients followed up for 15 years or more. Only 7% of the patients have been followed up for less than five years. Fifty-five patients died eventually from thyroid cancer.

Expected incidence and mortality from other malignancies

These have been estimated assuming that they are similar in thyroid cancer patients to those in the general population. A discussion of the basis of this assumption

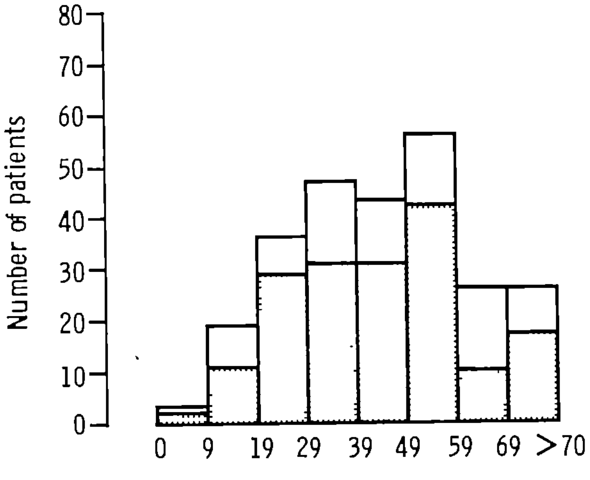

Fig. 1.

The patients of the follow-up according to age and sex. Stippled = female; open = male.

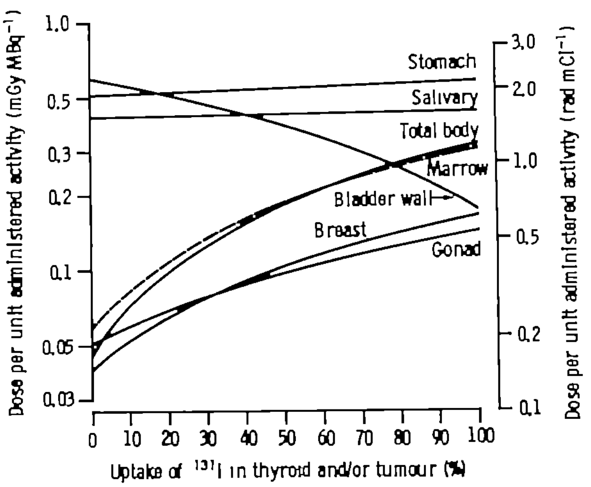

Fig. 2

Estimated irradiation doses to various organs derived from observations in the patients and a dosimetry model (Smith & Edmonds, 1984). The radiation dose received is expressed in relation to the fraction of the total administered activity that was concentrated in thyroid or tumour.

together with details of the methods for estimating expected incidence and mortality is given by Pochin (1969). The expected values for incidence and mortality from other malignancies were derived from age and sex specific rates. The values for incidence were obtained as the mean of those from the English registries reported in *Cancer Incidence in Five continents* (UICC, 1966; 1982). Values for mortality were obtained from the Medical Tables of the Registrar-General's Statistical Review of England and Wales, the average for those recorded in 1960 and 1973 being used as these were the years closest to the medians of the first and second, and of the third and fourth quartiles of the follow-up period.

Radiation dosimetry

The principles of the Medical Internal Radiation Dose Committee (Snyder et al, 1975) were used to calculate radiation doses to selected target organs.

The radiation dose to organs due to high-activity ^{131}I therapy of thyroid cancer depends on:

(1) Circulating radioiodine largely derived from the part of the administered ^{131}I activity which has not been concentrated by the thyroid or tumour;
(2) Organically bound ^{131}I released as a mixture of metabolites from normal thyroid or tumour tissue;
(3) Local concentration of ^{131}I in particular iodine-concentrating tissues, for example, thyroid, tumour, salivary glands, etc.;
(4) Radiation received by one organ from ^{131}I concentration in nearby organs.

On the basis of the available knowledge of the metabolism of the absorbed ^{131}I together with measurements of the concentration of ^{131}I in thyroid, tumour and other tissues, it is possible to estimate the radiation dose to various organs (Pochin & Kermode, 1975; Smith & Edmonds, 1984). In some organs of particular interest in this study, namely bone marrow, breasts and gonads, as well as the total body in general, the radiation dose received increases as the uptake in the thyroid and/or tumour increases (Fig. 2) This is due to the release of increased amounts of organic compounds of ^{131}I which provide the principal source of irradiation for these tissues. On the other hand, for urinary bladder, the irradiation comes chiefly from ^{131}I iodide contained in the urine which will be reduced if more ^{131}I is concentrated in the thyroid or tumour.

Hence the urinary bladder dose falls as the uptake in thyroid and/or tumour increases. The dose to the salivary glands is little influenced, largely because increased ^{131}I uptake in the neck provides a local source of radiation, so compensating for the reduced blood ^{131}I iodide The stomach dose depends mainly on the ^{131}I ingested and so is not appreciably influenced by variation of ^{131}I iodide in the blood. In the majority of patients who will already have had a thyroidectomy before the first treatment with ^{131}I, the fractional ^{131}I concentration in the thyroid remnant and tumour is usually low, being commonly less than 20%. The radiation dose received by the urinary bladder, stomach and salivary glands is therefore higher, usually being about 10 times as great as doses to other organs.

The results are given as means ± standard deviation.

RESULTS

Additional malignancies: incidence and mortality

A diagnosis of a second malignancy between one and 24 years after ^{131}I therapy was made in 18 patients (Table I) One patient had both a second and a third malignancy (a melanoma and a bronchial carcinoma). Four cases of leukaemia were originally believed to have occurred. One of these has however been excluded on further review as she had an aplastic anaemia with extensive multiple metastases of thyroid cancer and had no definite evidence of leukaemia at postmortem examination. All three patients with leukaemia (one considered as acute myeloblastic, two as lymphoblastic) presented within a few months of each other in 1957 and all had received considerable cumulative ^{131}I activity during the preceding years (Table I). No further cases of leukaemia have occurred since that time.

The products of the numbers of years at risk and of the estimated incidence and mortality rates (average of the 1960 and 1973 rates) were calculated for 5-year age intervals for each sex to give an expected incidence and mortality for our patients. At certain sites, in particular stomach, urinary bladder and salivary glands, high concentrations of ^{131}I occur. The expected incidences and mortalities for these sites have been included in Table II The p values represent the probabilities that the observed differences would be equalled or exceeded by chance, and were calculated from the Poisson distribution. Following Pochin (1969), we have estimated the statistical significance of the individual excesses taken in isolation. Thus, no allowance was made for the fact that five categories of second malignancy were considered, since there were grounds for predicting such malignancies on the basis of the known biokinetics and radiation dosimetry of ^{131}I. Although this does not apply to the sixth group (all other observed malignancies) the differences between observed and expected values were, in any case, not significant for this group.

Death from causes other than malignancy

Twenty-one patients (7 male, 14 female) have died from various causes unrelated to cancer, mainly from infections and cardiovascular disease. The average follow-up for these patients was 10.4 ± 5.9 years for males and 12.4 ± 7.3 years for females and they had been treated with 33 ± 13 and 28 ± 15 GBq (890 ± 363 mCi and 769 ± 405 mCi) ^{131}I respectively. Their ages at death were 75.1 ± 4.6 years for males and 76.3 ± 8.1 years for females compared with expected values (based on normal life expectancy of each individual at the time of diagnosis) of 78.4 ± 2.8 years and 82 ± 2.6 years respectively. The difference was only significant ($p < 0.02$) for females.

TABLE I

ADDITIONAL MALIGNANCIES IN PATIENTS PREVIOUSLY TREATED FOR THYROID CANCER

Site	Sex	Birth	First ^{131}I treatment	Total administered activity (GBq)	Radiation dose to relevant organ (Gy)	Diagnosis of 2nd malignancy	Death	Probable cause of death
Bladder	M	1909	1954	50	29	1974	1975	Ca bladder
	M	1928	1978	3.1	1.7	1981	—	—
	F	1923	1953	63	38	1967	1968	Ca bladder
Kidney	F	1904	1952	51	3.9*	1972	1972	Ca kidney
Breast	F	1895	1955	49	2.4	1957	1960	Ca thyroid
	F	1907	1963	27	1.4	1964	—	—
						1982	—	—
	F	1910	1958	57	4.5	1962	1963	Ca thyroid
	F	1921	1953	22	1.5	1967	—	—
	F	1927	1965	21	1.2	1981	—	—
Multiple myeloma	M	1927	1959	19	0.9*	1971	1973	Myeloma
Lymphoma	F	1910	1962	44	1.1*	1965	1969	Lymphoma
Malignant melanoma	F	1906	1952	24	1.4*	1962	—	—
Bronchus						1976	1976	Ca bronchus
Bronchus	M	1914	1950	10	0.7*	1971	1973	Ca bronchus
Stomach	F	1880	1953	36	18	1958	1958	Ca stomach
Larynx	M	1925	1963	3	0.1	1977	—	—
Leukaemia	F	1887	1954	53	3.2	1957	1957	Leukaemia
	F	1898	1954	42	2.8	1957	1957	Leukaemia
	F	1899	1953	65	4.6	1957	1958	Leukaemia

The radiation doses marked with an asterisk (*) are total body doses.

TABLE II

OBSERVED AND EXPECTED INCIDENCE AND MORTALITY OF OTHER MALIGNANCIES

	Patient-year-grays	Incidence Observed	Incidence Expected	*p*	Mortality Observed	Mortality Expected	*p*
Leukaemia	5.59×10^3 (marrow)	3	0.25	0.002	3	0.21	0.0013
Breast (females)	2.9×10^3	6	2.53	0.044	0	1.37	0.25 (NS)
Bladder	4.14×10^4	3	0.46	0.012	2	0.25	0.024
Stomach	3.68×10^4	1	1.1	0.17 (NS)	1	1.1	0.7 (NS)
Salivary glands	2.4×10^4	0	0.05	0.95 (NS)	0	0.01	0.99 (NS)
Other	4.9×10^3 (total body)	7	8.82	0.35 (NS)	5	6.67	0.66 (NS)
All malignancies		20	13.21	0.049	11	9.61	0.37 (NS)

NS = non-significant

Anaemia and neutropenia

Three patients (two women aged 53 and 59 years and one man aged 70) developed aplastic anaemia during treatment. All had extensive metastatic disease and had received repeated treatments, the total activities administered amounting to 63 (1700), 40 (1080) and 31 GBq (850 mCi) respectively. All patients died within 4 years of commencing therapy.

Fertility in young treated patients

Thirty female and 13 male patients were aged less than 30 years when they were first treated. The births in the families of those individuals who eventually married are given in Table III. Of the male patients, three are still unmarried; one was married for only one year and then divorced and another had a completed family at the time of treatment and did not plan to have more children. These five are therefore excluded. The remaining eight patients had a total of 15 normal children. The two youngest males, first treated when aged 15 and 17 years of age, subsequently had two and three normal children respectively. One man, aged 24 at first therapy in 1962, was treated with a total activity of 25 GBq (680 mCi) of ^{131}I, giving an estimated gonad dose of 1.4 Gy (140 rad). He subsequently married and has had no children, and investigations later for infertility showed persistent oligospermia together with elevated serum FSH concentration (22 mU/l). He has no history of any other possible cause of infertility.

Of the female patients seven of the 30 are not included in Table III as five had not married by the time of the review and a further two were from outside the UK and we have been unable to obtain the necessary information. The patient who received the

TABLE III

CHILDREN BORN TO 31 PATIENTS WHO HAD BEEN PREVIOUSLY TREATED WITH ^{131}I*

Age at first treatment (years)	n	Follow-up (y)	Live births	Total administered activity (GBq)	Estimated gonad dose (Gy)
Male patients					
10–19	2	13	2	36	1.9
		24	3	53	2.7
20–29	6	11.4±6.4†	10	19±6.3	1.1±0.4
Female patients					
< 10	1	32	3	1.9	0.1
10–19	6	16±4.6	12	21±15	1.3±0.8
20–29	16	11.3±6.5	14	14±9.8	0.8±0.5

*Only patients treated before the age of 29 years and who intended to have children are included.
†mean ± SD

TABLE IV

PATIENTS WITH PERSISTENT SALIVARY GLAND PROBLEMS AFTER HIGH ACTIVITY ^{131}I THERAPY

Patient no.	Sex	At first treatment Age	Year	Total administered activity (GBq)	Estimated salivary gland dose (Gy)	Diagnosis in salivary glands
1	F	23	1952	41	21	Benign pleomorphic adenoma
2	F	42	1979	8.5	2.8	Chronic sialoadenitis
3	M	32	1970	16	6.1	Parotid mass (unoperated)

highest activity was aged 19 years in 1963 at the first treatment. The total activity she received was 44 GBq (1200 mCi), giving an estimated gonad dose of 2.55 Gy (255 rad). She subsequently had two normal children, the first being born four years after completion of therapy. Three patients have been investigated for infertility. They were 14, 26 and 28 years old at the time of their commencing ^{131}I treatment and received total activities of 30 GBq (810 mCi) in 1962–65, 3.7 GBq (100 mCi) in 1978 and 9.3 GBq (250 mCi) in 1969 respectively. The estimated gonad doses for these patients were 1.7 (170), 0.2 (20) and 0.6 Gy (60 rad) respectively.

Salivary glands

Pain in one or more of the salivary glands, especially the parotid, occurred in about 10% of our patients at some time after ^{131}I therapy with high total activities. Often the symptoms did not begin until some months, even years, after commencing therapy. In the majority, spontaneous improvement took place in a few weeks or months without any specific treatment. Occasionally the symptoms were more persistent with recurrences of pain and swelling for a year or more but in only three patients did nodules develop within the salivary glands (Table IV). Patient 3 had a firm mass of about 2 cm diameter in the left parotid which gave him no discomfort and has remained unchanged for four years.

Pulmonary metastases and lung irradiation

Diffuse pulmonary metastases were present in five patients, all with papillary tumours which concentrated ^{131}I (Table V). The follow-up of these patients is from 8 to 17 years and only one has had any evidence of respiratory impairment. The latter (patient 5) when first treated in 1966 at the age of 12 years had miliary metastases widely disseminated in both lungs; she was below the third percentile in growth and development. She received a total ^{131}I activity of 14 GBq (380 mCi). Chest X-ray appearances were improved but a full remission was not induced. Total chest ^{131}I concentration remained at between 2 and 4% of the administered activity indicating persistent functional chest metastases. Further therapies were not given as treatment no longer appeared to effect any significant improvement in ^{131}I uptake or in the radiological appearance. Her general well-being was good and normal growth and development occurred. She subsequently married and although of limited exercise tolerance has had three pregnancies (two normal children, one stillbirth). Respiratory function has remained persistently impaired with evidence of gradual deterioration over the years. Full vital capacity in 1968 was 1.1 l (expected 2.2 l) and in 1978 and 1982 was 1.05 l (expected 3.6 l) and 0.76 l respectively. Gas diffusion as measured by carbon monoxide was also much reduced, the most recent value being 4.83 mmol.min^{-1} kPa^{-1} l^{-1} (expected value 9.6). Extensive pulmonary metastases were also present in a boy of seven years old (patient 4). Treatment successfully eliminated the lung disease and his physical development has been normal. Seventeen years after treatment he has a normal chest radiograph and respiratory function.

Patient-year-grays (PYG)

The probable excesses of incidence and mortality shown in Table II can be considered in relation to the radiation doses received by the respective organs. For this purpose, values of patient-year-grays were calculated for relevant organs by the method of Pochin (1969). For each patient and all administrations of ^{131}I, the estimated organ radiation doses were multiplied by the period of follow-up and the values were summed to give the total number of patient-year-grays (PYG) for each organ (Table II). In addition to those listed, the PYG values for gonads were 3.6×10^3 for females and 1.0×10^3 for males. Values of PYG were calculated on the assumption that all of the ^{131}I administration to a

TABLE V

PATIENTS WITH BILATERAL DISSEMINATED PULMONARY METASTASES

Patient no.	Sex	At first treatment Age	Year	Total administered activity (GBq)	Estimated pulmonary dose (Gy)
4	M	7	1965	17	28
5	F	12	1966	14	8.2
6	M	15	1969	36	2.4
7	F	27	1971	17	0.6
8	F	34	1974	25	11

TABLE VI

INFERRED RISK RATES PER 10^4 PATIENT-YEAR-GRAYS TO ORGANS (WITH 95% POISSON CONFIDENCE LIMITS)

Second malignancy	Incidence	Mortality
Leukaemia	4.9 (0.7 to 15.2)	4.9 (0.7 to 15.3)
Breast cancer (females)	12.0 (−1.1 to 36.4)	−4.7 (−4.7 to 8.0)
Bladder cancer	0.7 (0.04 to 2.0)	0.4 (0 to 1.7)
All malignancies except leukaemia	8.2 (−6.2 to 29.1)	−2.9 (−12.0 to 13.1)

given patient occurred at the commencement of the follow-up period and are therefore overestimated for patients given multiple administration. Since the mean follow-up period for our patients was 11.2 years and ^{131}I administrations were given at variable intervals after the start of treatment which had a weighted mean of about 1.7 years, the actual PYG values will be approximately 85% of those given.

Inferred risk rates, in terms of excess incidence or mortality for the various second malignancies per 10^4 PYG to the respective organs, are shown in Table VI. The ranges of values estimated from the 95% Poisson confidence limits for the numbers of observed second malignancies are also given.

DISCUSSION

Of the few patients who died from causes other than cancer, the expectation of life of the females appeared to be slightly, though significantly, reduced. They had all received high total activities of ^{131}I and it is possible that such exposure may have a nonspecific deleterious effect.

In addition, some organs carry an *a priori* expectation of increased cancer risk on account of their ^{131}I concentrating properties or because they are especially exposed during absorption and excretion of ^{131}I. When these organs were considered individually, the excess of leukaemia and of bladder cancers was apparent. The patients who died with these malignancies had been treated in the early years of the clinic (1953–54) when therapy was more aggressive and all had received a total activity in excess of 40 GBq (1100 mCi). The time interval between the deaths from leukaemia and ^{131}I treatment was short, averaging only three years, while in the case of the bladder tumours, the interval was considerably longer, 14 and 20 years. This is generally in line with previous experience of radiation effects in which the minimal latency period for leukaemia was about two years and for solid cancers about 10 years (Kohn & Fry, 1984). Hoffman et al (1982), reviewed a group of 1005 women treated with ^{131}I for hyperthyroidism and found an increased relative risk of cancer in the organs that concentrate ^{131}I which was greatest in the first five years after treatment and diminished progressively in subsequent years. They also noted that there was a suggestive increase of relative risk for bladder cancer but not for leukaemia.

The incidence of breast cancer in our patients was also possibly increased although so far no increased mortality is evident. This was also apparent in the earlier study (Pochin, 1969). Although the lactating breast concentrates iodine we have seen no evidence from scanning that the quiescent breast does so and, as a result, the estimated radiation doses received by breast tissue were all relatively low (Table I). Possibly some association between breast and thyroid disease, such as has been previously postulated (Chalstrey & Benjamin, 1966) underlies these observations.

On the assumption that the observed excess mortality can be wholly attributed to the effects of radiation, 2.8 excess cases of leukaemia correspond to a rate of 4.9 cases per 10^4 PYG or, since the mean follow-up period was 11.2 years, of 55 (8-171) per 10^4 patient-Gy during the period of observation. The ICRP (1977) risk factor for leukaemia is taken to be 20 per 10^4 Sv, so our result does not greatly differ from this value, despite our three observed cases being clustered in one year. From our results, mortality from bladder cancer has an inferred risk-rate of 0.4 cases per 10^4 PYG, if assumed to be radiation-induced, corresponding to 4.5 (0–19) cases per 10^4 patient-Gy during the observation period. This suggests an average risk factor for bladder cancer of similar magnitude to that used by ICRP (1977) for bone and thyroid cancer mortality. The risk factor used by ICRP (1977) for breast cancer mortality is 25 per 10^4 Sv, for purposes of radiation protection. However, as this is an average value incorporating a negligible risk for males, it is more appropriate to consider a risk factor of 50 per 10^4 Sv for females. Since breast cancer is about 50% fatal, the implied incidence in females is about 100 per 10^4 Sv. We observed no excess mortality from breast cancer, but the excess incidence was significant with an inferred risk rate, if radiation-induced, of 12 cases per 10^4 female PYG corresponding to 137 (−13 to 417) cases per 10^4 female patient-Gy during the observation period.

Of the 31 younger patients who wished to have children, 13% did not conceive during the follow-up period—a figure comparable to that of 12% observed by Sarker et al (1976) in their follow-up of 40 young patients treated with ^{131}I for thyroid carcinoma. Thus there was no definite evidence of any decrease in fertility but the radiation doses to the gonads, particularly in some males was in the range known to produce impaired spermatogenesis, at least transiently (Speiser et al, 1973; Lushbaugh & Casarett, 1976; Ash, 1980). Handelsman and Turtle (1983) have recently demonstrated that dose-dependent damage to spermatogenesis, usually transient, may follow ^{131}I therapy at high activity. One of our male patients was infertile and had persistently elevated plasma FSH and oligospermia but two other patients, who had received even larger amounts of activity during their teenage years, both fathered normal children subsequently.

There may therefore be some individual variation in this risk.

Damage to lung function resulting from pulmonary fibrosis has been reported as following ^{131}I treatment for diffuse pulmonary metastases (Rall et al, 1957). Only one of our patients (patient 5) with diffuse pulmonary disease had significant respiratory impairment but she also had persistent extensive metastatic disease over many years. It was not possible therefore to be sure of the relative importance of the metastases and the irradiation. It is probably relevant that the two patients of Rall and his associates who had severely impaired pulmonary function were similarly affected in having extensive and persistent pulmonary metastases. By contrast, another of our group, patient 4, who received at least as much pulmonary irradiation as patient 5, had eventually complete remission of his disease, and moreover, has had no detectable respiratory impairment. The continuing presence of metastatic disease rather than lung irradiation may be chiefly responsible for the respiratory impairment.

As iodide is concentrated in the secretion of the salivary glands, these glands receive considerable irradiation during ^{131}I therapy. Mild symptoms were not infrequent after treatment but in three patients (a little over 1%) persistent masses occurred and biopsy was felt necessary in two. No malignancies were detected and there was no evidence that the salivary glands suffered any permanent or serious damage.

The results of several follow-up studies indicate that the prognosis and survival of patients with differentiated thyroid cancers are improved by radioiodine therapy, particularly for older patients and for those with metastases (Leeper, 1973; Tubiana et al, 1975; Maheshwari et al, 1981). It is therefore reassuring to see that the present observations show the relatively low risk of high activity ^{131}I therapy. The benefits of therapy do not appear to be outweighed by long-term harmful effects. The risk of cancer of the bladder and possibly leukaemia does however appear to be increased, especially when many repeated high-activity treatments are given. Fertility in younger male patients may also be adversely affected, although this is most unlikely to be permanent with the activities usually employed now in younger patients. Treatment with high-activity ^{131}I should, especially in younger individuals, be at the lowest level for effective control. Initial total thyroidectomy and constant consideration of the surgical alternatives for persistent or recurrent lesions are important ways of achieving this object.

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Book reviews

Cell Clones—Manual of Mammalian Cell Techniques. Ed. by C. S. Potten and J. H. Hendry, pp. xi+235+index, 1985 (Churchill Livingstone, Edinburgh), £45.00
ISBN 0–443–02805–2

This book is essentially a laboratory manual describing in great detail the existing techniques for studying the properties of "clonogenic cells" in mammalian tissues. There are 25 chapters, written by "authors who have had some first-hand experience of using the techniques". The methods described range from the widely used (such as clonogenic survival assay of cells growing as established lines in culture and assay of haemopoietic spleen colony-forming units) to the much less well known (such as those for clonal regeneration in cartilage and the thyroid gland).

The introduction and the first chapter, dealing with the concept and the mathematical basis of colony growth and clonal regeneration, are particularly well written. They should be read and comprehended by any newcomer to the field before moving on to specific techniques. The individual chapters are generally clear and contain a wealth of useful experimental detail. I would, however, have liked to see in each chapter a specific section dealing with "problems which arise with this technique and practical solutions to them". The authors give a variable amount of acknowledgment to the existence of such problems.

The book will be of most value to those entering the field of experimental radiobiology. With this in mind it is a pity that several of the graphs still have the radiation dose expressed in rads. Some authors have relabelled the axis when reproducing previously published figures; I think they all should have done so. This book will still be much used at a time in the future when the rod (sic) (legend to Fig. 2.1) is as widely used as the pole and the perch. The editors suggest in the introduction that "these techniques could be useful in several fields aside from radiobiology". I would be very interested to know what exactly they had in mind. The book seems to me to be destined for an extremely limited audience.

This will certainly become the standard reference work on the techniques described and the editors are to be congratulated in bringing it about. To anyone about to use any of these techniques, my advice would be to read about it, see it in operation, and then attempt it, in that order.

PETER TWENTYMAN

Gynaecologic Cancer By Arlene A. Forastiere, pp. viii+307, 1984 (Churchill Livingstone, New York), £36.00
ISBN 0–443–08274–X

This is very much an American book. It talks of radium used for "intra-cavity therapy" and doses measured in "mg hrs", and afterloading techniques are dismissed in a few lines in the past tense. It is nonetheless stimulating and well written, with a wealth of references, albeit predominantly to authors in the USA. The editor wisely did not plan to cover all topics, but concentrated on the main areas of controversy and interest.

I particulary liked the chapter on chemotherapy for carcinoma of the cervix, which includes chemotherapy given before radiotherapy for advanced disease. It is clear that this is a potentially valuable technique, but it requires further investigation into the interaction of radiotherapy and chemotherapy, and optimum timing of the two modalities in relation to late (rather than early) morbidity and tumour control.

Ovarian carcinoma is well covered, but with scant enthusiasm for the benefits of radiotherapy and a persistent conviction that second-look laparotomy is an important part of general management. Again, in the section on endometrial carcinoma, the author (a gynaecologist) takes a very pessimistic view of the value of post-operative radiotherapy in early but poor risk cases (poorly differentiated tumours with deep myometrial invasion or involvement of the cervix). His concern as to whether the high risk of late radiation morbidity is justified would not be echoed by many British oncologists.

The epidemiology of both cervical and endometrial carcinoma is very well covered and the chapter on carcinogenesis following alkylating agents and radiation therapy is novel and has some useful references.

In general, the book will be of particular interest to oncologists experienced in managing gynaecological malignancy because of the detailed and well referenced discussion on controversies. However, those who are new to the subject may, despite the excellent summaries, be confused. It is a useful book to have in the library.

THELMA D. BATES

1986, *The British Journal of Radiology*, 59, 53–59 JANUARY 1986

Thermal enhancement of radiation damage in previously irradiated mouse intestine

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ABSTRACT

The effects of prior irradiation (8 or 10 Gy of X rays) on the response of mouse jejunum to a test treatment of (a) hyperthermia (42 0°C for 60 min), (b) X rays (8 or 10 Gy) or (c) combined hyperthermia and radiation were investigated at various times up to 7 months after the primary treatment Tissue injury was quantified by crypt survival 4 days after the test treatment.

Although tissue susceptibility to direct thermal injury was increased 10–15 days after irradiation, neither radiation sensitivity nor thermoradiosensitisation were significantly affected at any of the time intervals used The results support the concept that there are different pathways for the *in vivo* expression of gross thermal damage and thermoradiosensitisation

Clinically, hyperthermia is often used to treat tumours which have recurred some time after more conventional therapy, and the possibility of recall of an earlier treatment becomes of special relevance if normal tissues included in the treatment field cannot be adequately cooled during subsequent hyperthermia Although Perez et al (1984), reviewing results with local microwave hyperthermia, have reported a "satisfactory" tolerance of normal tissues to heat, the majority of comparative clinical evaluations of hyperthermia have used superficial tumours, in which the heating field can be well defined and the surrounding skin actively cooled during therapy.

Experimentally, residual damage can be assessed either by a functional assay or by modification of the "dose" required at retreatment. In several studies on rodent skin (Law & Ahier, 1982, Wondergem & Haveman, 1983; Baker et al, 1983) and one on small intestine (Hume & Marigold, 1982), an increase in the cytotoxic effect of hyperthermia has been demonstrated several weeks to months after X irradiation. The clinical relevance of this finding remains unclear. The biological rationale for using thermoradiosensitisation of tumours as an alternative to the direct cytotoxic effect of heat has been well documented (e.g. Field & Bleehen, 1979; Overgaard, 1982). In contrast to the effects of prior irradiation on direct heat damage, recent studies on rodent skin have suggested that the ability of hyperthermia to enhance radiation injury appears to be little affected by pre-treatment with X rays (Wondergem & Haveman, 1983; Baker et al, 1983; Law et al, 1985).

In the present study, we have investigated the degree of thermal enhancement of X-ray damage to small intestinal mucosa of mouse at various times, up to 7 months, after prior irradiation. The work complements the earlier paper on direct thermal cytotoxicity in pre-irradiated intestine (Hume & Marigold, 1982).

METHODS

Female Parkes mice (NIMR, Mill Hill) were treated at 10 to 12 weeks of age whilst anaesthetised with sodium pentobarbitone, initially given intraperitoneally at 0.07 mg g^{-1} body weight. Four mice were used for each treatment

Hyperthermia

Local hyperthermia was achieved by immersion of an exteriorised loop of jejunum (approximately 10 cm long) in heated Krebs-Ringer solution The bathing fluid was stirred continuously such that the temperature around the intestine was maintained to within 0.1°C of that required. In sample mice, the jejunal temperature was also monitored, using fine thermocouples implanted in the intestinal wall. The mesentery and vasculature were kept intact and, after heating, the exteriorised loop was replaced in the peritoneal cavity and the wound sutured. Full details of the technique have been reported by Hume et al (1979a).

Irradiation

All irradiations were carried out using a Pantak industrial X-ray machine operating at 240 kVp (filtration 0.25 mm Cu, 1.00 mm Al, HVL 1 12 mm Cu). For the primary treatments, the intestine was irradiated *in situ* by ventro-dorsal exposure of the abdomen, at a dose-rate of 1.50 Gy min^{-1}. The remainder of the animal was shielded with 3 mm-thick lead. For the second, test treatment a jejunal loop (approximately 10 cm long) was irradiated whilst exteriorised. The mice rested on their sides in small open-ended containers covered with 3 mm-thick lead. The intestinal loop, marked with a stitch at each end, was positioned horizontally on a perspex plate and covered with gauze, soaked in warm sterile saline (0.9%), and a raised perspex lid. With the ambient temperature controlled to 24±1°C, the temperature around the intestine was approximately 28°C. The X-ray dose-rate was 2.04 Gy min^{-1}.

Assay

Damage to the clonogenic compartment of the mucosa was quantified using the assay for radiation injury developed by Withers and Elkind (1970), in which numbers of regenerating crypts are counted 3.5–4 days after treatment. In the present work, two samples of jejunum (each 2 cm long) were taken from the treated length and fixed in Bouin's solution. At least eight non-serial transverse sections (5 μm-thick, haematoxylin and eosin stained) were prepared per mouse. In the majority of cases, crypt counts were made over a 1 mm length of jejunal circumference diametrically opposite to the mesenteric blood vessel attachment. In this region, the local temperature during hyperthermia is known to equilibrate to a temperature 0.1°C below that of the bathing fluid (Hume et al, 1979b).

Experimental plan

In the main series of experiments, a primary X-ray treatment of 8 or 10 Gy was followed at various times (from 10 days to 7 months) by a test treatment of (a) hyperthermia alone, (b) X rays alone, (c) hyperthermia followed immediately by X irradiation, or (d) X rays followed immediately by hyperthermia.

Since two methods of irradiation were used, the tissue response following each was checked in a preliminary experiment. The results are given in Fig. 1. In our hands, crypt sensitivity was similar irrespective of whether intestine was irradiated whilst exteriorised or *in situ* and, in the latter case, whether the mice were anaesthetised or restrained. The primary X-ray doses of 8 or 10 Gy caused a reduction in crypt number to approximately 90% and 70% of control, respectively. Figure 2 illustrates that, although there was some increase in crypt number over days 4–10 after treatment, recovery was not complete until approximately 50 days. When the test treatment was given during the period of partial recovery, the tissue response was corrected for any residual reduction in crypt number by expressing the results as a percentage of age-matched control or primary-treated animals.

For all time intervals except 52 days, only two test X-ray doses were used because of the large numbers of mice needed for full crypt survival curves. The relatively mild treatments of 8 and 10 Gy were chosen because of the marked radiosensitising effect of hyperthermia (see Fig. 5). For the two-modality treatments, the interval between irradiation and hyperthermia was approximately 2 min. The hyperthermal treatment was constant at 42.0°C for 60 min.

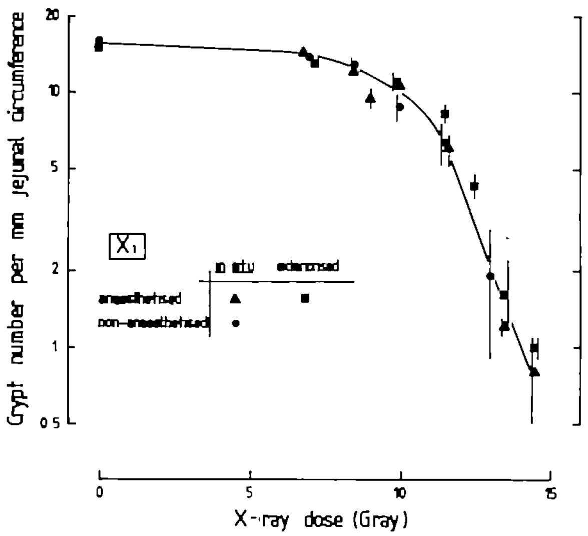

FIG. 1.

Dose-response curves for crypt survival assayed 4 days after X irradiation of mouse small intestine. X rays were given either to an exteriorised loop of jejunum (■) or to the intestine *in situ*, in which case the mouse was either anaesthetised (▲) or restrained (●) Crypt counts were made over 1 mm lengths of jejunal circumference, immediately opposite to the mesenteric attachment, but similar results were obtained when the assessment was made adjacent to the mesentery. The zero dose values are from sham-irradiated animals Values are means with standard errors from at least 4 mice. Where not indicated, the error was within the size of the symbol

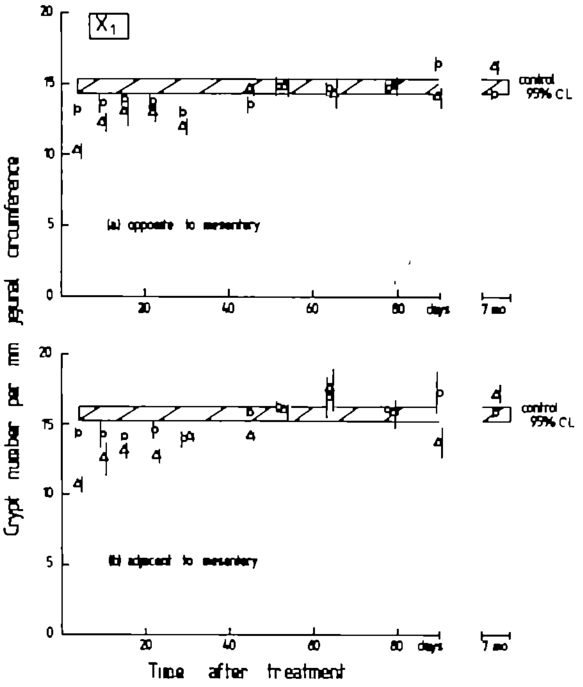

FIG. 2.

Recovery of crypt number following a primary X-ray treatment of 8 (○) or 10 Gy (△) to jejunum irradiated *in situ* (X_1) Crypt counts were made over a 1 mm length of circumference either (a) opposite or (b) adjacent to the mesenteric attachment The hatched band represents 95% confidence limits about the mean control value from age-matched untreated animals. Data points are means with standard error bars from 4 mice

RESULTS

(a) *Single-modality test treatments*

Hyperthermia When given alone, the test heat treatment used in the present experiments (42.0°C for 60 min), was far below that required to cause crypt loss. Previous work has demonstrated that, using 42 0°C, a heating time of 90 min is required before a significant loss of crypts can be measured (Hume & Marigold, 1985) and that a 50% reduction in crypt number occurred one day after a heating period of approximately 180 min (Hume et al, 1979a). As illustrated in Fig. 3, a marked increase in thermal susceptibility was observed following each primary X-ray dose, such that crypt number was reduced by approximately 60%. This increase occurred over a longer interval following 10 Gy but, in each case, the thermal response returned to the subthreshold level from 20 days to 7 months after the primary irradiation.

Irradiation. Tissue response following single test X-ray treatments of 8 or 10 Gy did not vary significantly over the 7 months of the experiment and have therefore been expressed as mean values (the hatched bands in Fig. 4). As shown in Fig 4, neither an 8 Gy nor a 10 Gy pre-treatment significantly affected crypt loss following either of the test treatments used.

(b) *Two-modality test treatments*

The thermal enhancement of crypt loss following X irradiation of rodent small intestine has been described previously as primarily due to a reduction in the shoulder of the crypt survival curve (Merino et al, 1978, Hume & Marigold, 1981; Gibbs et al, 1984). In the present experiments, hyperthermia caused both a reduction in shoulder and an increase in slope. This is illustrated in Fig. 5, which shows dose-response curves for crypt survival following X rays given either alone or immediately preceded by hyperthermia at 42.0°C for 60 min.

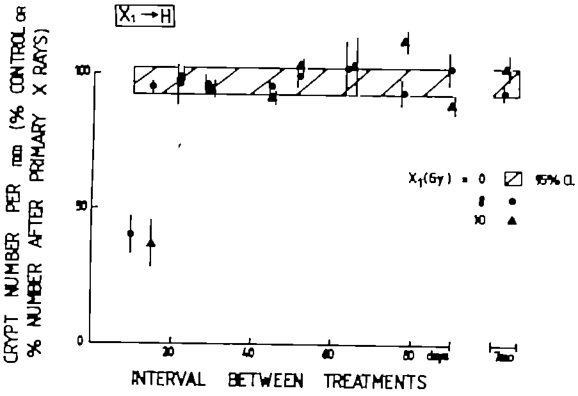

FIG. 3

Crypt number 4 days after a heat treatment of 42 0°C for 60 min (H) Hyperthermia was given at various times after an X-ray dose of either 8 (●) or 10 (▲) Gy (X_1) The hatched band represents 95% confidence limits about the mean hyperthermal response in age-matched but previously untreated animals The data points are means, with standard error bars

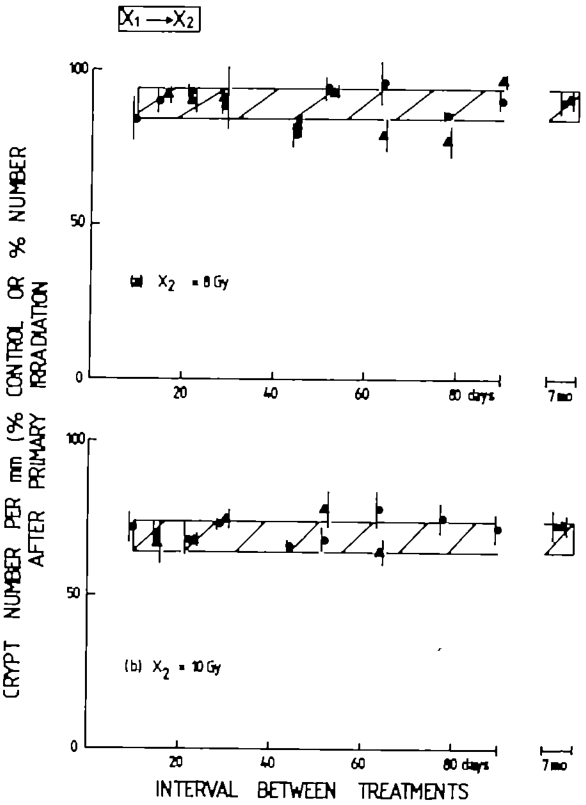

FIG 4.

Crypt number 4 days after a radiation dose of either (a) 8 Gy or (b) 10 Gy This test X-ray treatment (X_2) was given at various times after a primary X-ray dose of either 8 (●) or 10 (▲) Gy (X_1) The hatched bands represent 95% confidence limits about the mean radiation responses in age-matched, previously untreated animals. The data points are means, with standard error bars, from 4 mice. Some groups were omitted because of the limited number of animals surviving the acute reaction following the higher of the two primary treatments, there were no "late" deaths.

Also from Fig. 5, it can be seen that crypt survival following the two-modality treatment was not significantly affected by radiation given 52 days prior to the test treatment. The thermal enhancement ratio (TER, defined as the ratio of X-ray doses which cause the same level of tissue injury when given with or without hyperthermia (Robinson et al, 1974)) was calculated to be 1 4 at the 30% crypt survival level.

For all other intervals between primary and test treatments investigated, only two test radiation doses were used, namely 8 and 10 Gy. Figures 6 and 7 show crypt loss following two-modality test treatments for

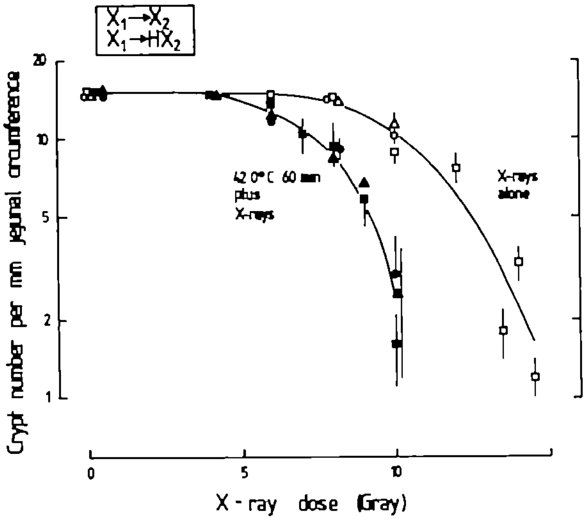

FIG 5.

Dose-response curves for crypt survival assayed 4 days after X irradiation of a jejunal loop X rays were given either alone (open symbols) or immediately after a heat treatment of 42.0°C for 60 min (closed symbols) The test treatments were given 52 days after a primary X-ray dose of 8 Gy (○, ●) or 10 Gy (△, ▲) or to age-matched, previously untreated animals(□, ■). The data points are means, with standard errors. Where not indicated, the error was within the size of the symbol.

"heat → X rays" and "X rays → heat", respectively. Although thermal enhancement was less using the latter sequence, the increase in response compared with that following X rays alone is clearly seen for both radiation doses, at each time interval. There was no consistent or primary-dose dependent change in the degree of thermal enhancement for either sequence of modalities. The data points marked with an asterisk are from treatments which resulted in a marked increase in the response to hyperthermia alone (see Fig. 3) and therefore contain a component of direct thermal damage, also manifest as crypt loss.

DISCUSSION

In the clinic, late radiation damage to small intestine may be expressed many months or years after radiotherapy and is manifest as ulceration, with haemorrhage, obstruction and perforation (reviewed by Novak et al, 1979). In mouse, Peck and Gibbs (1984) have recently described a progressive, dose-dependent chronic injury, measured as an increase in "elastic stiffness", beginning two weeks after single X-ray doses greater than approximately 10 Gy, four months after a dose of 8 Gy and eight months after a dose of 6 Gy. In addition, histological changes (primary collagen deposition and diffuse oedema within the submucosa) have been described by Reynaud and Travis (1984), 6 and 12 months after 9 or 11.5 Gy.

We have previously described a marked, but transient, increase in the hyperthermal sensitivity of mouse intestine, developing several days after X-ray doses greater than 6 Gy (Hume & Marigold, 1982). For example, the tissue response to a heat treatment of 43.0°C for 35 min was increased to a maximal value between 1 and 2 weeks after 9 Gy and remained above control for approximately 2 months, despite the apparent morphological and clonogenic recovery of the mucosa. This decreased tolerance to hyperthermia has also been reported in rodent skin (reviewed by Hume, 1985) and could well be due to exacerbation of thermal injury by stromal or vascular changes following the initial radiation treatment. In this context, Falk (1984) has recently described long-term vascular disturbances in mouse small intestine following 9 Gy, manifest as partial occlusion of, and reduction in length of, the

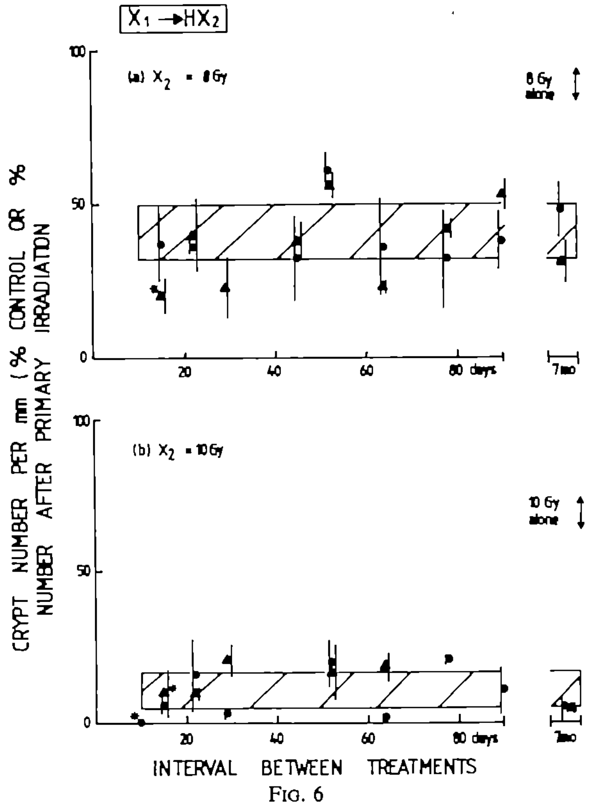

FIG. 6

Crypt number 4 days after a two-modality test treatment comprising 42.0°C for 60 min followed immediately by either (a) 8 Gy or (b) 10 Gy The test treatment (HX_2) was given at various times after a primary X-ray treatment of either 8 Gy (●) or 10 Gy (▲) (X_1). The hatched band represents the mean response (with 95% confidence limits) in age-matched, previously untreated animals The data points are means, with standard error bars Those marked with an asterisk correspond to treatments after which direct thermal damage was expressed (see Fig 3).

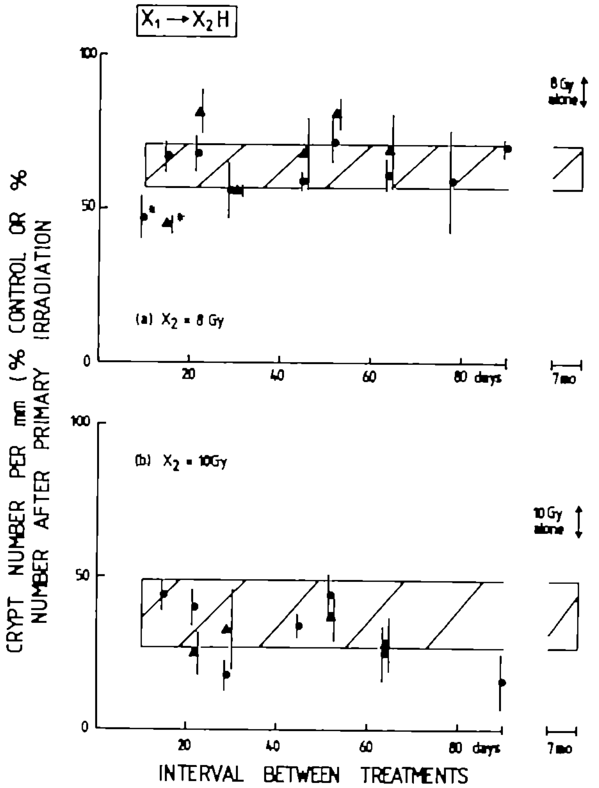

FIG. 7

Crypt number 4 days after a two-modality test treatment of either (a) 8 Gy or (b) 10 Gy followed immediately by 42.0°C for 60 min (X_2H). The symbols and hatched band are as described in Fig 6.

venous vascular tree. The increase in susceptibility to direct thermal injury following pre-treatment with X rays has been confirmed in the present study (Fig 3).

In contrast, crypt tolerance to radiation was not significantly affected by prior irradiation, at least using the test doses of 8 and 10 Gy. Recently, Reynaud & Travis (1984) have reported both a decrease in clonogenic crypt cell sensitivity (an increase in D_0) and an increase in shoulder of the cell survival curves, beginning two months after 9 Gy, and suggest that this is due to radiobiological hypoxia within the crypts.

The reasons for the differences between this finding and that of the present study remain unclear. In a small, additional experiment illustrated in Fig. 8, we investigated crypt survival following 8 or 10 Gy given 7 months after a primary X-ray treatment of 11 or 12 Gy, in addition to 8 or 10 Gy, and assessed crypt number "per total circumference" in addition to "per mm length" in the four quadrants of the circumference. As can be seen, there was no significant effect of the primary treatment, for any of the assessments used. Moore and Maunda (1983) have described a lower (but statistically insignificant) radiation sensitivity in anti-mesenteric compared with mesenteric crypts, possibly due to small variations in oxygen tension, and it was felt that any changes in relative radiobiological hypoxia due to pre-treatment would be most apparent in the regions diametrically opposite to the mesenteric vasculature attachment. It should be noted, however, that the exteriorisation technique used in the present experiments could result in direct diffusion of oxygen into the tissue from the bathing solution, masking any effects of vascular inadequacy. In addition, the microcolony assay system has a relatively large inherent variability (see Potten et al, 1983) and it is possible that the restricted use of only two radiation test treatments was insufficient to identify any small changes in crypt survival.

The major part of the present study was designed to investigate the effect of prior irradiation on the ability of mild hyperthermia to enhance the acute tissue response following a second dose of X rays. When given alone, the hyperthermal treatment (42.0°C for 60 min) was insufficient in itself to cause crypt loss. When given immediately prior to X rays, the calculated TER value of 1.4 was similar to that reported previously (Hume & Marigold, 1985). The slightly lower thermal enhancement obtained using the reverse sequence of modalities (Fig 7 compared with Fig. 6) has been described for several rodent normal tissues (reviewed by Law, 1982). It is possible that the difference is due to modification of the microenvironment by prior hyperthermia in addition to any interaction between radiation-damage and hyperthermal-damage repair pathways. (The mechanisms involved in hyperthermal radiosensitisation have been reviewed by Dewey, 1983.)

Test X-ray doses of 8 and 10 Gy were chosen to give tissue responses following thermoradiosensitisation which resulted in four crypt survival levels, ranging between approximately 65% and 10% of control. Although the response to the combined treatment was apparently increased at times when the tissue response to hyperthermia was increased (*i.e.* 10 days after 8 Gy and 15 days after 10 Gy), this increase could, in general, be accounted for by the additional decrease in crypt number due to heat alone. Interpretation of the results with regard to thermoradiosensitisation is, however, difficult since there is some evidence to suggest that, at least in small intestine, TER values approach unity when the tissue expresses a significant amount of direct thermal injury (Hume & Marigold, 1981).

At all other time intervals used, the hyperthermal treatment remained subthreshold for crypt loss and the thermal enhancement of radiation injury was unaltered, irrespective of the sequence of modalities in the test treatment. As stated earlier, it has been suggested that one reason why thermal enhancement *in vivo* is greater for the H → X sequence than for the X → H sequence is that thermal modification of the microenvironment at the time of irradiation (*e.g.* in blood flow and oxygen tension, as demonstrated in mouse skin by Morris and Field (1979)) causes a modification of radiation

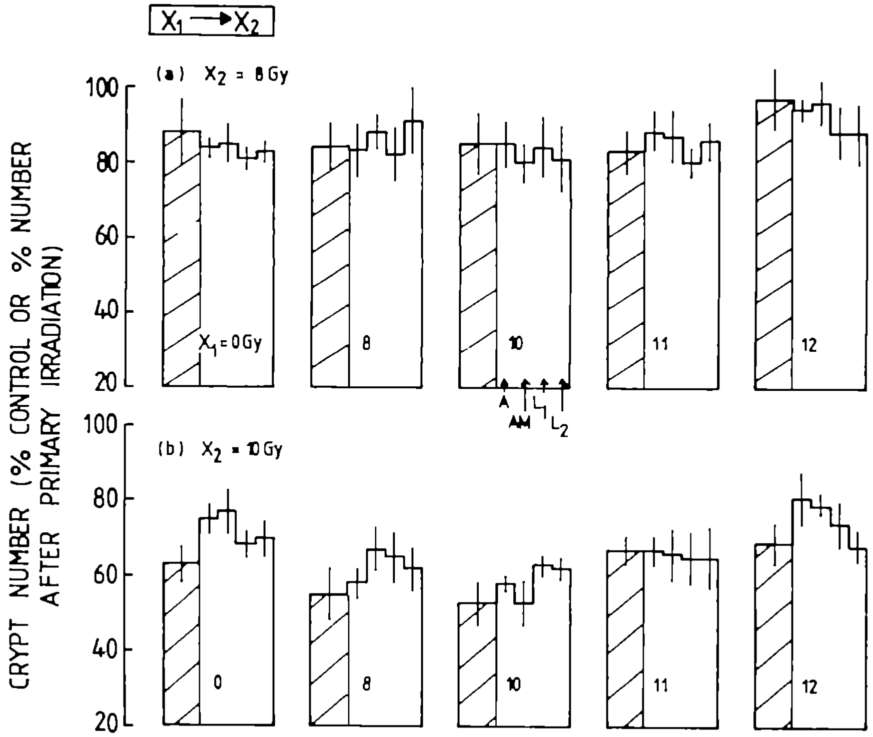

Fig 8.

Crypt number 4 days after (a) 8 Gy or (b) 10 Gy of X rays (X_2) given 7 months after an X-ray treatment of 8, 10, 11, or 12 Gy (X_1), or to age-matched controls For each treatment group, crypt number is expressed either per jejunal circumference (hatched bars) or per mm circumference (open bars). In the latter case, the counts were made either adjacent to the mesenteric attachment (A), diametrically opposite to the mesentery (AM), or in the two lateral quadrants (L_1 and L_2), as indicated Values are means with standard error bars

sensitivity. It might, therefore, be expected that any residual or progressing tissue change following the primary X-ray treatment, which resulted in an increased thermal cytotoxicity, would have also increased the thermal enhancement factor for the H → X sequence. This was not the case.

The lack of effect of prior irradiation on thermoradiosensitisation has also been reported for mouse skin (Wondergem & Haveman, 1983; Baker et al, 1983; Law et al, 1985). It appears that when hyperthermia is used with radiation in therapy as an interactive rather than a complementary modality, then the tolerance of normal tissue is similar in pre-irradiated and previously untreated sites. The results support the view that, *in vivo*, the cytotoxic effect of heat and thermoradiosensitisation are expressed via different pathways.

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Book reviews

Imaging Anatomy of the Head and Spine. By H M. Snitzlein and F. R Red Murtagh, pp 324, 1985 (Urban & Schwartzenberg, Baltimore and Munich), £149.95.
ISBN 0-8067-1881-1 (USA)
3-541-71881-1 (Munich)

The rapid developments in diagnostic imaging over recent years have demanded that the radiologist has a knowledge of anatomy not only in the now familiar transverse axial plane of conventional CT, but also in the multiple and various planes displayed by magnetic resonance imaging (MRI) and CT reformations Keeping pace with these technical advances has proved a challenge to radiological textbooks and this book admirably meets this challenge, providing an anatomy reference text which is appropriate to a modern imaging department.

The format of the book is well described by its subsidiary title, "A photographic colour atlas of MRI, CT, gross and microscopic anatomy in axial, coronal and sagittal planes". The first half of the book is devoted to anatomy of the brain, with coloured illustrations of gross and microscopic sections matched to corresponding CT and MR images. Scans of patients and cadaver specimens have been used, and a plain skull radiograph is marked with a cursor to indicate the plane of the section illustrated. A short text covering pertinent anatomical features is given in each section. There are chapters on the anatomy of the orbit and larynx, and the anatomy of the temporal bone is particularly well illustrated by high-resolution CT displayed on extended scale. The cerebral ventricular system is covered in some detail and basic vascular anatomy illustrated in the form of line diagrams, is included. The section devoted to the spine follows a similar style, with cadaver sections matched to CT and MRI. The MR images are presented in both the transaxial and sagittal planes in the cervical region but only the transverse plane in the lumbar spine The multiple CT sections through various levels of the cervical spine are repetitive in the anatomical structures shown.

Each chapter concludes with a short list of references which refer mainly to other anatomical textbooks or major review articles The index is very comprehensive, with sometimes up to thirty-five page references for individual anatomical structures, which might seem excessive but is inevitable in a text of this nature

The illustrations are excellent The format of the book is similar to others on the market but the anatomy is given in much greater detail, perhaps more detail than one actually requires in everyday practice However, this is an advantage and an important feature now that considerably more anatomical detail of the brain can be demonstrated by MRI than before The authors and publishers are to be congratulated on producing a very high quality and beautiful textbook It would make a useful reference text in a radiological department with a neuroradiological bias and with both CT and MRI facilities. It is relatively expensive and might well be beyond the resources of most departments in this country

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Ultrasonics for Medical Applications (2) (Acta Electronica, Vol 26, Nos 1/2) pp. 132, 1984 (Acta Electronica, Limeil-Brevannes, France), US$30 00.
ISBN 0001-558X

Quantitative tissue characterisation—the remote *in vivo* categorisation of tissue type and pathology on an objective basis—has for some time been a subject of active research interest in the context of ultrasound More recently, a parallel interest has developed in the field of NMR, and it is already clear that the two modalities will show some intriguing similarities whilst each has some particular strengths and weaknesses. It is probably the case that the fundamental physical phenomena underlying the various ultrasound approaches are more complex and less well understood than those on which NMR methods depend and, in the short term, this situation may result in the more rapid development and application of the latter. The volume under review is a special issue of a journal, bringing together a set of mainly theoretical papers, several from French authors who seldom publish in English, that discuss various aspects of the basis of ultrasonic tissue characterisation The publication will make a useful contribution to the specialist literature on the subject, and to resolving some of its conceptual difficulties, but the more general reader will find little here to indicate the considerable extent to which practicable methods of ultrasonic tissue characterisation are already being developed and tested in clinical trial.

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The RBE for mouse bladders after irradiation with 1 to 8 fractions of d(4) + Be neutrons

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ABSTRACT

Mouse bladders were irradiated with 1, 2, 4 or 8 fractions of electrons or neutrons. Urination frequency was scored from 9 to 14 months after irradiation and this was used as a measure of the extent of bladder damage.

The RBE for neutrons relative to 1.8 MeV electrons increased from 3.2 for large single doses to 5.4 for 8 fractions.

Repair of sublethal injury after electron irradiation was considerable, with 63–72% of each fractionated dose repaired. Repair after neutron irradiation was less, with only 35–43% of each fractionated dose recovered

Linear-quadratic analysis of all the fractionated bladder data yielded an α/β ratio for electrons of 6–7 Gy and, surprisingly, the α/β ratio for neutrons was only slightly higher at about 8 Gy

Loco-regional recurrence of bladder tumours after treatment with conventional radiotherapy is still a common problem (*e.g.* Laramore et al, 1984). Due to the high incidence of local recurrence, preoperative radiotherapy followed by cystectomy is often performed (Wallace & Bloom, 1976; Whitmore et al, 1968, 1977; Miller, 1977). This type of treatment is, however, associated with the complete loss of a normal bladder and loss of sexual function. Recently, alternative therapies are being explored, including the use of radium implant needles for T1 and T2 bladder tumours (Batterman & Tierie, 1985), or the use of a hypoxic radiosensitiser in combination with radiotherapy in an attempt to overcome tumour hypoxia and to improve local control (Awwad et al, 1984). Another approach is the use of high LET radiation such as neutrons (Batterman et al, 1981; Laramore et al, 1984; Pointon et al, 1985). Some of these studies (Batterman & Breur, 1981) have shown fast neutrons to be effective in the control of bladder cancer, but severe late normal tissue injury occurred as a result of underestimating the RBE for late damage.

There is now both clinical and experimental evidence to suggest that higher RBEs may be obtained in slowly dividing tissues, *i.e.* those which give rise to late normal tissue damage, than in rapidly dividing tissues which are responsible for acute radiation injury (Hussey et al, 1982, Ornitz et al, 1980; Van der Kogel et al, 1982; Terry & Denekamp, 1984, Withers et al, 1978, 1982) Much more data are required to enable an accurate prediction of RBEs in such tissues at low, clinically relevant, doses per fraction since it seems probable that an RBE of 3.0, which is commonly used as the basis for dose adjustment in neutron trials, may not be high enough to prevent serious late complications (Laramore et al, 1979, Hornsey, 1980, 1982).

The present study was designed to measure the RBE for bladder damage after 1 to 8 fractions of neutrons relative to electrons. In addition to measuring RBE, the extent of repair of sublethal injury after neutron irradiation was measured and compared with that occurring after low LET radiation.

MATERIALS AND METHODS

The bladders of female mice were irradiated with either 1.8 MeV electrons or neutrons of mean energy 3 MeV. Specific pathogen-free mice, of the strain CBA/Ht Gy f BSVS, were used at 10 to 12 weeks of age when they weighed 20 to 26 g. Mice were anaesthetised by an intraperitoneal injection of 60 mg/kg sodium pentobarbitone 10 minutes before each irradiation. The irradiation field size for both neutrons and electrons was 20 × 12 mm and the bottom margin of this field was located directly over the pubic symphysis. Doses quoted refer to the peak dose at the centre of the field. For all irradiations the entire volume of the bladder plus part of the underlying uterus and rectum were included in the field. For electron irradiation, however, the rectum received only 60% of the bladder dose due to the sharp fall-off of electron dose in tissue (Stewart et al, 1978).

Irradiation with electrons was carried out using a pulsed beam from a linear accelerator of 1.8 MeV nominal energy and the average dose-rate was 112.5 Gy min^{-1}. Animals were irradiated at 1 m distance from the electron window of the accelerator in order to ensure a uniform distribution across the field. Full details of the electron irradiation set-up and dosimetry were given in an earlier publication (Stewart et al, 1978).

Neutrons of mean energy 3.0 MeV (maximum energy 8.4 MeV) were produced from the Gray Laboratory Van der Graaf accelerator by bombarding a thick beryllium target with 4 MeV deuterons. The target-to-skin distance was 40 cm and the dose-rate was 0.55 Gy min^{-1}. Dosimetry was carried out according to the European protocol for neutron dosimetry (Broerse et al, 1981). The gamma contamination of the beam was 10.8% and all doses refer to the neutron-only dose, as measured in ICRU muscle-equivalent material.

After both electron and neutron irradiations mice were given 20 mg/kg bemigride injections to aid recovery from the anaesthetic. Groups of 8 animals per dose were irradiated with single doses or with 2, 4 or 8 fractions of either neutrons or electrons given in an overall treatment time of 14 to 18 days.

After the end of the treatment period mice were stored without testing for 9 months, although they were checked daily for general health status. From 9 to 14 months all surviving animals were tested for urination frequency at monthly intervals. Frequency was measured over a 24-hour period by placing the animals in special cages with wire bar floors beneath which absorbent paper was drawn at a speed of 15 cm h^{-1}. At the end of each test period the number of discrete urinations was counted under an ultraviolet lamp which caused the urine to fluoresce and thus facilitated counting. The mean frequency of urination for groups of irradiated animals (±1 SEM) is used as a measure of the extent of bladder damage.

At 14 months the urine volume output per mouse was estimated by measuring the area of individual urine spots on the frequency sheets The total "area" could be converted into a urine volume by referring to a previously constructed calibration curve (Stewart et al, 1981). A few mice were found to have a very low output of urine which was significantly below that of age-matched controls (< 0.5 ml/24 h compared with 1.0–1.5 ml in controls); this correlated with post-mortem findings of severe hydronephrosis and/or calcareous bladder deposits blocking the urethra. The frequency responses of such mice were excluded from the last test at 14 months.

Autopsies were performed on all surviving animals at 14 months. The macroscopic incidence of hydronephrosis, bladder calculi, bowel damage and tumours was noted; however, these autopsies did not extend to histological examination and the quoted tumour incidence may be an underestimate.

Results

The urination frequency of control animals was between 5 and 11 voidings per 24 hours (mean 7.2±0.9) over the entire period of 9 to 14 months. Previous studies (Stewart et al, 1978) have demonstrated that urination frequency is not increased until at least 6 months after irradiation and that the maximum response does not occur until 9 to 12 months. In the present series of experiments frequency was only slightly increased at 9 months and much better dose-effect responses were obtained at 11 months; these data are shown in Fig. 1. Each panel illustrates results for a separate fractionation schedule and the RBEs*, calculated at a urination frequency level of 22 spots per day, are indicated on each graph. For most of the fractionation schedules it was possible to construct well defined dose-effect curves for both electrons and neutrons at 11 months. The 2-fraction electron arm of this experiment was, however, virtually unusable. One complete dose group was lost before testing when a leaking water bottle flooded the cage and the frequency responses of the remaining groups were very variable (possibly due to some transient infection). For these reasons we have used data from a previous 2-fraction electron experiment (Stewart et al, 1984a) for comparison with the 2-fraction neutron data, although the current data are also shown (closed circles, Fig. 1). RBE values were estimated by comparing the electron and neutron doses required to give the same level of damage (Table I). The RBE for bladder damage at 11 months increased from 3.1 for single doses of 23 Gy electrons, to 4.8 for 8 fractions of 7 Gy per fraction (electron dose).

Measurement of organ function at a single time point

TABLE I

RBE values for mouse bladder

No of fractions	Total isoeffective dose (Gy) (Dose range from envelope of standard errors on dose-effect curves) electrons	neutrons	RBE (+1 SEM)
1	(a) 23 (18–30)†	7.5 (7–8.5)	3.07±0.85
	(b) 24 (18–30)	7.5 (7.2–7.9)	3.20±0.81
2*	(a) 35 (33–39)	11.0 (9–12)	3.18±0.51
	(b) 35 (33–39)	9.1 (8.7–9.4)	3.85±0.68
4	(a) 46 (45–48)	11.5 (9–13.5)	4.0 ±0.79
	(b) 48 (46–49)	10.8 (9.9–11.2)	4.44±0.39
8	(a) 55 (50–66)	11.5 (10–16)	4.78±1.43
	(b) 65 (63–>65)	12.0 (10–15.3)	5.4 ±1.32

Doses to produce a urination frequency of 22 spots/24 hours at (a) 11 months, (b) 11–14 months.
* Electron data are from a previously published experiment (Stewart et al, 1984a).
† Figures in brackets represent 1 standard error.

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*RBE = Relative Biological Effectiveness = $\frac{\text{low LET dose}}{\text{neutron dose}}$ for an equivalent level of damage.

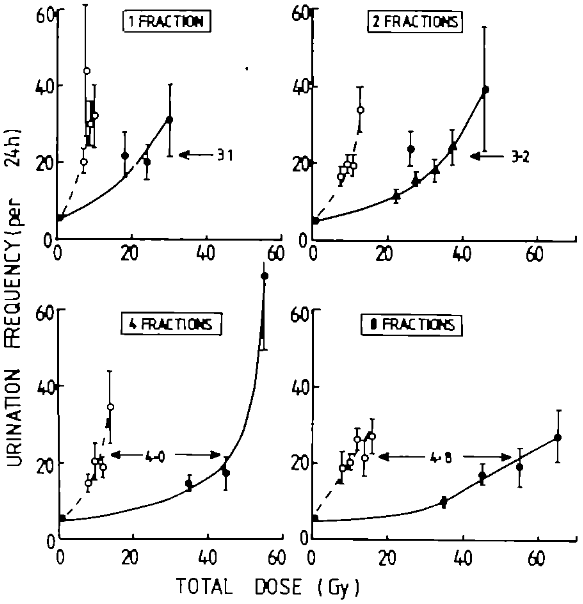

FIG. 1.

Dose-effect curves for increased urination frequency 11 months after irradiation of the bladder with electrons (●) or neutrons (○). Two-fraction data from a previously published electron experiment (see text) are also shown (▲). Each data point represents the mean (±SEM) number of urinations in a 24-hour test period for a group of 4 to 7 mice. The RBE at a level of 22 urinations/24 hours is indicated beside each pair of curves.

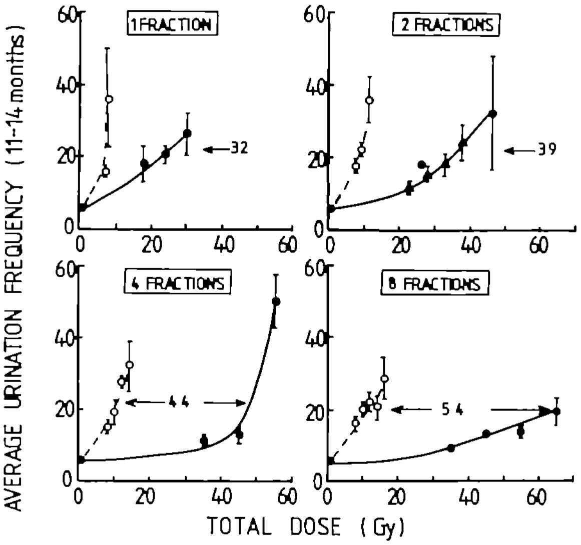

FIG 2

Dose-effect curves for urination frequency averaged over the period 11 to 14 months after irradiation with electrons (●, ▲) or neutrons (○). The RBE at a level of 22 urinations per 24 hours is indicated for each fractionation schedule.

(*e.g.* 11 months) may not give a complete indication of the relative amounts of damage caused by neutrons and electrons. It is possible, for example, that the rate of development of damage after the two types of radiation could be different. We have therefore averaged the results obtained for urination frequency at 11 to 14 months (four separate tests) and these average frequency values are shown in Fig. 2. RBEs can again be determined by comparing the neutron and X-ray curves and slightly higher RBEs are suggested (3.2–5.4) than from the data for 11 months only (Figs. 1 and 2, Table I). These differences are, however, not significant.

In order to illustrate the dose-sparing effect of fractionation, the urination frequencies after 1–8 fractions of electrons or neutrons are shown separately in Fig. 3 and 4. It is clear that the total electron dose (Fig. 3) required for a given level of damage increased markedly as the fraction number increased from 1 to 8. The amount of repair of sublethal damage can be calculated from the dose displacement of the fractionated curves relative to the single dose response. Repair increments, and the fraction of each dose recovered (F_R), were calculated from both 11-month data and the average values over 11 to 14 months (see Table II). Repair after electron irradiation was extensive, increasing from 63% to 72% of each dose recovered as the dose per fraction decreased from 17.5 to 8 Gy. Electron dose-response curves, and the corresponding estimates of repair, at 11 months were very similar to those obtained using averaged data over the period 11–14 months.

Figure 4 shows neutron dose-response curves, after 1–8 fractions, at 11 months (top panel) or averaged data for the period 11–14 months (bottom panel). At 11 months there was a clear separation of the 1- and 2-fraction curves but little further dose sparing with increasing fractionation. This would suggest that only after high doses was there a significant capacity for repair of neutron damage. However, when all the data from 11 to 14 months are considered (bottom panel, Fig. 4), there is some indication of additional repair (*i.e.*, increased total dose) as the number of fractions increases from 2 to 8. The proportion of each dose recovered (F_R) increased from 35% after 2 doses of 4.5 Gy to 43% after 8 doses of 1.5 Gy (see Table II).

At 14 months all surviving animals were sacrificed and a macroscopic autopsy was performed. Approximately 10% of the mice died before testing (*i.e.*, within 9 months of irradiation) and in these animals the cause of death was generally severe intestinal inflammation or ulceration. The incidence of rectal stenosis was low, with only two obvious cases out of 190 treated animals. In a previous series of experiments (Stewart, 1978) there was a higher incidence of rectal stenosis (16%) after single electron doses of 20–30 Gy. Hydronephrosis and calcareous deposits in the bladder were the most common post-mortem findings. After electron irradiation there was a 19% incidence (12/64) of cystic kidneys

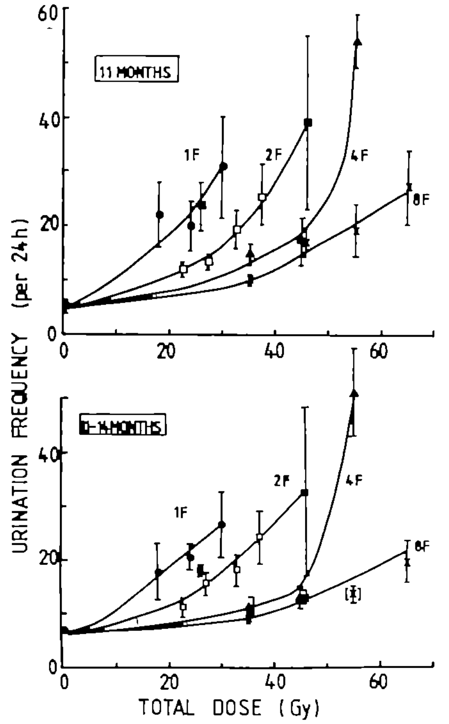

Fig. 3.

Dose-effect curves for urination frequency after 1 to 8 fractions of electrons at 11 months (top panel) or 11 to 14 months (bottom panel). ● = 1 fraction; ■ = concurrent two fraction experiments; □ = data previously published (see text); ▲ = 4 fractions; × = 8 fractions The 8-fraction value in brackets is the mean of only two animals. All other dose points represent the mean value (±SEM) for four to seven mice.

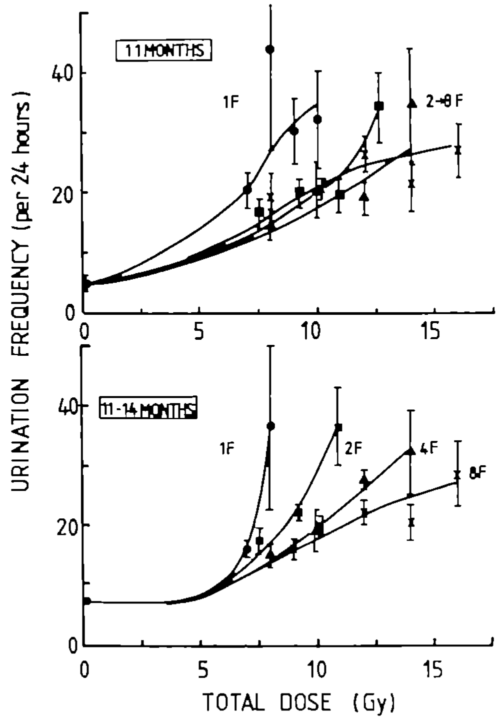

Fig. 4

Neutron dose-effect curves for urination frequency at 11 months (top panel) and 11 to 14 months (bottom panel) after irradiation of the bladder with 1 to 8 fractions. ● = 1 fraction, ■ = 2 fractions, ▲ = 4 fractions; × = 8 fractions

and 22% of the animals (14/64) had calcareous bladder deposits at the time of sacrifice After neutron irradiation the incidence of hydronephrosis and bladder calculi was 17% (16/95) and 24% (23/95) respectively (*i.e.*, insignificantly different from those seen after electron irradiation) Tumours were found in the liver, rectum, mesenteric adipose tissue, bladder and kidney. The total incidence of macroscopic tumours after electron irradiation was 8% (5/64), and after neutrons was 16% (15/95) This difference was again not significant. The tumour incidence in a group of 37 control animals of the same age, sex and strain was previously found to be 8% (Stewart, 1978); no tumours were seen in the six control animals from the current experiment.

Discussion

Relative Biological Effectiveness (RBE)

The RBE for neutrons has long been known to increase with decreasing size of the dose per fraction (Fowler & Morgan, 1963; Field, 1969). This is due to the shape of the X-ray (or other low LET) radiation dose-effect curve rather than the neutron curve which is essentially linear over the dose range of interest (Withers et al, 1982). The shape of the X-ray dose-response curve is believed to have greater curvature for late normal tissue damage than for acute damage (Thames et al, 1982), and therefore higher RBEs would be predicted for late normal tissue damage. Experimental and clinical evidence using multiple small fractionated doses generally bears out this prediction (Hussey et al, 1980, 1982; Ornitz et al, 1980, Geraci et al, 1977; Van der Kogel et al, 1982), although early experimental results with fewer, larger fractions did not demonstrate a higher RBE for late damage (Field & Hornsey, 1971).

In the present series of experiments the minimum dose per fraction was 4–8 Gy electrons (8F schedule). Assuming an RBE of about 0.85 for electrons relative to 250 kV X rays (Lindop & Rotblat, 1961), these doses are equivalent to 3.4 to 6.8 Gy X rays. This is still considerably in excess of the doses per fraction used clinically and it is quite possible that the *observed* maximum RBE of 4.8–5.4 (4–4.6 after correction for electron RBE) would be even higher at lower doses per fraction. A continued increase in RBE at doses per fraction below 5 Gy has been demonstrated using many other normal tissue systems such as spinal cord

(Hornsey, 1982; Van der Kogel et al, 1982), lung (Hornsey, 1982; Parkins et al, 1985), late skin fibrosis (Hussey et al, 1982), acute skin reactions (Joiner et al, 1983), colon and rectum (Terry & Denekamp, 1984) and small intestine (Geraci et al, 1977).

The RBEs measured for bladder damage from the 8-fraction experiments agree well with published values, for 3 MeV neutrons for kidney (Stewart et al, 1984c) and colorectum (Terry & Denekamp, 1984), *i.e.*, RBEs of 4–5 at X-ray doses per fraction of around 5 Gy. These values are, however, slightly higher than have been reported for lung, using 3 MeV neutrons, and for spinal cord and late skin fibrosis, using higher energy neutrons, at equivalent doses per fraction (Hussey, 1982; Hornsey, 1982; Van der Kogel et al, 1982; Parkins et al, 1985). Even allowing for the scatter observed in the bladder data (Figs. 1 and 2), which gives rise to an error on the RBE estimates of up to 30%, it seems clear that the RBE for mouse bladder is considerably greater than 3 at a relatively high dose per fraction of 5 Gy

Repair of sublethal damage

The maximum overall treatment time used in this experiment was 18 days. Previous thymidine labelling studies have demonstrated that compensatory proliferation is not initiated in the bladder epithelium before 3 months (Stewart et al, 1980; Stewart, 1985). Split-dose experiments with 2 fractions given in overall times of 1 day to 1 month have also demonstrated that there was no additional dose sparing when the fraction interval was extended beyond 24 hours (Stewart et al, 1981). It is therefore assumed that all the dose sparing which was observed in these experiments as the number of fractions increased is the result of repair of sublethal radiation damage.

The increase in total dose required for a constant level of bladder damage with fractionation is shown in Fig. 5. Data from previous experiments with up to 20 fractions of electrons have been added (closed symbols) to give a well defined bladder isoeffect curve for electron irradiation. The present data agree well with the previous values and it is clear from the electron isoeffect curve (Fig. 5) that no single exponent for fraction number, N, can be determined in the equation:

$$\text{Total dose} = \text{NSD} \times N^x \times T^y \text{ (Ellis, 1969)}$$
$$\text{where } T = \text{overall time.}$$

The exponent for N decreases from a high value of 0.5 between 1 and 2 fractions to 0.24 between 10 and 20 fractions. A similar reduction in exponent with increasing fraction number has been reported in other normal tissues (Douglas & Fowler, 1976; Field et al, 1976; Hornsey et al, 1975; Parkins et al, 1985; Stewart

TABLE II

REPAIR OF SUBLETHAL RADIATION DAMAGE IN MOUSE BLADDER AFTER ELECTRONS OR NEUTRONS

Dose (Gy) to produce isoeffective levels of damage				$\frac{D_N - D_1}{(N-1)}$*, Gy	F_R†
1	2	4	8		
Electrons					
(a) 23					
(b) 24					
	(a) 35			12 ± 6.1	69%
	(b) 35			11 ± 6.7	63%
		(a) 46		7.7 ± 2.1	67%
		(b) 48		8 ± 1.5	67%
			(a) 55	4.6 ± 1.4	66%
			(b) 65	5.9 ± 0.9	72%
Neutrons					
(a) 7.5					
(b) 7.5					
	(a) 11.0			3.5 ± 1.68	64%
	(b) 9.1			1.6 ± 0.50	35%
		(a) 11.5		1.3 ± 0.79	46%
		(b) 10.8		1.1 ± 0.30	41%
			(a) 11.5	0.6 ± 0.12	41%
			(b) 12.0	0.6 ± 0.40	43%

Doses to produce a urination frequency of 22 spots/24 hours at (a) 11 months and (b) 11–14 months Errors are ± 1 SEM

* D_N = total dose in N fractions, D_1 = dose in 1 fraction,

$$\dagger F_R = \frac{(D_N - D_1)/(N-1)}{\text{dose per fraction}}$$

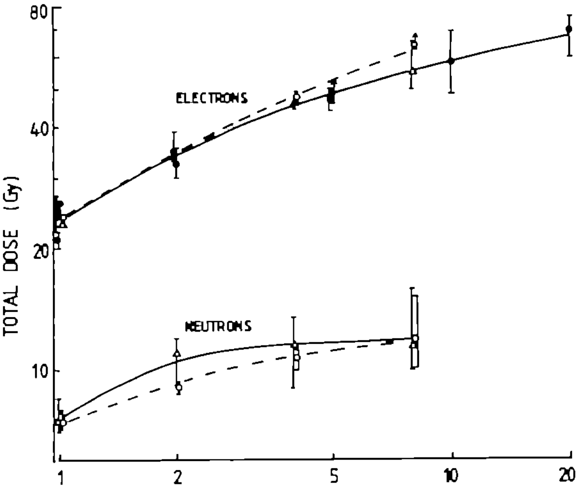

Fig. 5.

Total isoeffective doses required to increase the urination frequency to a level of 22 events per 24 hours △ = 11 month data, ○ = average values 11–14 months; ● = previously published electron data (Stewart et al, 1984).

et al, 1984b) and is to be expected if the data conform to a linear-quadratic model (Thames et al, 1982). Isoeffective neutron doses increased much less sharply with fractionation although there was a significant increase in total dose required for 2 fractions compared with that for a single dose. For further fractionation the total neutron dose was either the same (measured at 11 months, open triangles, Fig. 5), or was slightly increased (all data, averaged over 11 to 14 months, open circles). This demonstrates that repair of sublethal damage did occur after large doses of neutrons and that some further repair was possible by using multiple small doses. The discrepancy between isoeffective doses for neutrons measured at 11 months or 11 to 14 months is due to the fact that the neutron damage was not fully expressed at 11 months. The dose-effect curves consequently steepened slightly at later times after neutrons but not after X rays.

The data shown in Figs. 1 and 2 have also been analysed in terms of a linear-quadratic expression for damage. In Fig. 6 reciprocal isoeffective doses for electrons (top panel) or neutrons (bottom panel) are plotted against dose per fraction; note the different scales for the two sets of data. This transformation allows a determination of the ratio α/β in the linear-quadratic equation:

$$\text{Effect} = \alpha d + \beta d^2 \quad \text{(Douglas \& Fowler, 1976)}$$

The ratio α/β is an important parameter since it defines the curvature of the radiation dose-response curve; it is the dose at which cell killing by the linear and quadratic terms in the equation are equal.

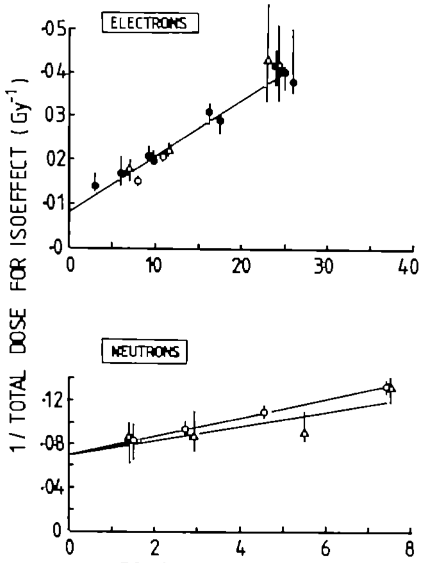

Fig 6.

Reciprocal total dose versus dose per fraction for a response level of 22 urinations/24 hours. Symbols are as for Fig. 5. Lines through the data points were obtained from a linear regression analysis Note the difference in scales for both ordinate and abscissa between the electron and neutron panels.

The electron data from the current experiments (open symbols), plus previously published results (Stewart et al, 1984a, closed symbols), give a good fit to a straight line ($p > 0.95$). The α/β ratio can be determined using the intercept to estimate α and the slope to estimate β. A linear regression analysis of all electron data, including single doses, gives a value of 5.9 ± 0.6 Gy for the ratio α/β; however a higher value, 7.0 ± 1.4 Gy, is obtained when single-dose values are omitted from the analysis. Electron data from the present experiments therefore support previous results (Stewart et al, 1984a) and confirm that, although the bladder is a slowly dividing tissue, the α/β ratio is rather higher than has been observed in other late-responding tissues (Barendsen, 1982; Fowler, 1984; Thames et al, 1982; Withers et al, 1982).

Reciprocal total doses for the neutron data are shown in the bottom panel of Fig. 6. Separate linear regression lines are drawn through the data for 11-months only (triangles), and data for the average frequency response during the period 11–14 months (circles). The intercept (which is proportional to α) is very much higher than for electron irradiation (0.071 compared with 0.008 Gy^{-1}). LET-dependent changes in α by factors of at least 7 have previously been reported for skin, colon/rectum, lung and kidney (Joiner et al, 1983; Stewart et al, 1984c). Such an increased value for α after high LET radiation demonstrates that the initial single-

TABLE III

LINEAR-QUADRATIC ANALYSIS OF BLADDER DAMAGE USING THE EQUATION. EFFECT $(E) = \alpha d + \beta d^2$

	Electrons		Neutrons	
	All data	Excluding single doses	All data	Excluding single doses
α/E (Gy^{-1})	0.007 74	0.008 509	0.0707	0.0694
β/E (Gy^{-2})	0.001 306	0.001 211	0.008 37	0.008 88
α/β (Gy)	5.92 ± 0.59	7.0 ± 1.4	8.45 ± 0.30	7.82 ± 0.29
Predicted max RBE $= \alpha_n/\alpha_e$	9.1	8.2		
Predicted min. RBE $= \sqrt{(\beta_n/\beta_e)}$	2.5	2.7		

The above parameters were calculated using the isoeffective doses for 22 urination events per day over a testing period of 11 to 14 months

hit component of damage is much more effective for high LET than low LET radiation. It is difficult to determine accurately the slope of this neutron line with only four data points (Fig. 6) but from a linear regression analysis α/β ratios of 8.4 Gy (11–14 month data) to 10.2 Gy (11-month data) are suggested. This represents a very small increase for neutrons compared with the α/β ratio of 6–7 Gy measured for electron irradiation of the bladder. This is a rather surprising finding since similar studies in skin, kidney, colo-rectum and lung (Joiner et al, 1983; Stewart et al, 1984c; Terry & Denekamp, 1984; Parkins et al, 1985) have all demonstrated an approximately 10-fold increase in the α/β ratio for 3 MeV neutrons relative to X rays. These changes in α/β ratio were entirely due to the change in the α component since the β component was remarkably similar after the two types of radiation. In the present studies the large increase in α for neutrons is in agreement with reports for other normal tissues but the correspondingly high β value after neutrons contrasts with findings in all other tissues.

It is possible to use the linear-quadratic equation to predict minimum and maximum RBE for any tissue in which the dose-response curves for damage can be fitted by a linear-quadratic expression. If we assume that the radiation injury in bladder can be fitted by such an expression (see Fig. 6 and Table III) then the maximum RBE for bladder at low radiation doses is given by the ratio of α for neutrons to electrons. Similarly the minimum RBE for large doses of radiation is given by the ratio of $\sqrt{\beta}$ for neutrons to electrons. Using the α and β values from a linear regression analysis of the data shown in Fig 4 we obtain a limiting low-dose value for bladder RBE of 8–9.

In conclusion, the measured RBE for bladder damage in mice increased from 3.2 for large single doses to 5.4 for doses per fraction of 4 to 6 Gy. The predicted maximum RBE for low doses of less than 1 Gy is between 8 and 9.

ACKNOWLEDGMENTS

We would like to thank Drs. J. F. Fowler, J Denekamp and B. D. Michael for their many helpful discussions in the planning and writing up of this work We are also grateful to Mr B. Hall and the Van der Graaf team of the Gray Laboratory for assistance with the neutron irradiation, Jos Olijve for her efficient typing of the manuscript, and Mr. P. Russell and colleagues for breeding and care of the animals. The project was entirely financed by the Cancer Research Campaign, England

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1986, *The British Journal of Radiology*, 59, 69–74 JANUARY 1986

Case reports

Generalised enchondromatosis associated with haemangiomas, soft-tissue calcifications and hemihypertrophy

By *E. M. D. Phelan, M.B., D.M.R.D., H. M. L. Carty, F.R.C.P.I., F.R.C.R. and †S. Kalos, F.R.C.S.
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(*Received March 1985*)

The manifestations of generalised enchondromatosis are multiple enchondromas in the metaphyses of long and short tubular bones, and in flat bones. The skull and vertebrae are relatively spared. The changes are usually bilateral but asymmetrical. The association of enchondromatosis with haemangiomas in Maffucci's syndrome is well known, but unusual manifestations of enchondromatosis are increasingly described. Spranger et al (1978) described two types, one with multiple enchondromas of the long, tubular bones and flat bones, with generalised irregular dysplasia of the vertebral bodies, but only minimal involvement of the phalanges; the second type consisting of generalised evenly distributed enchondromas with severe involvement of the hands and feet, mild platyspondyly and skull deformity.

Van Creveld et al (1971) described metaphyseal chondrodysplasia calcificans, which is now accepted as a variant of generalised enchondromatosis. Kaibara et al (1982) described generalised enchondromatosis with haemangiomas and soft tissue calcifications.

We describe a similar case of generalised enchondromatosis, haemangiomas, soft tissue calcifications and also hemihypertrophy, (which has not previously been seen in association with enchondromatosis), in a child who first presented at age three months with progression up to the age of 14.

CASE REPORT

The boy (Fig. 1), was born in November 1969 by Caesarian section following a normal pregnancy. His birth weight was 2.8 kg. There was no history of drug ingestion during pregnancy, the parents are not consanguineous, there is no relevant family history, and he has a normal brother.

At birth, haemangiomas were noted on the back and abdomen. A lump on the dorsum of the left foot increased gradually in size, and he was referred for X-ray examination at the age of three months.

The limbs were found to be short relative to the trunk, the left leg was shorter than the right and the hands were trident-shaped (Fig. 2).

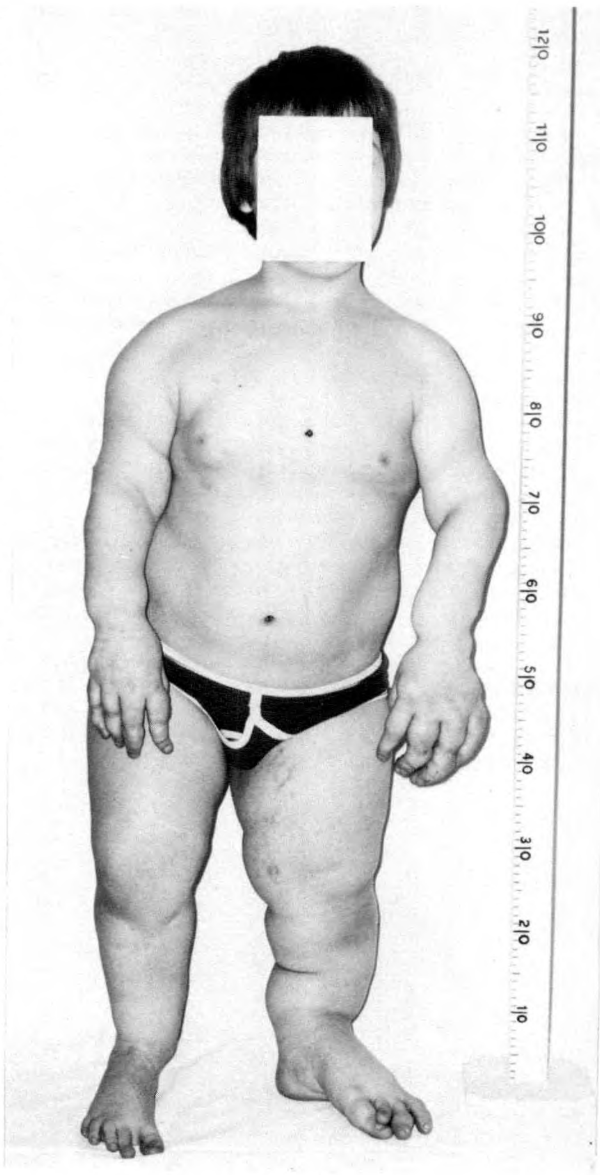

FIG. 1.
Age 13 years 4 months.

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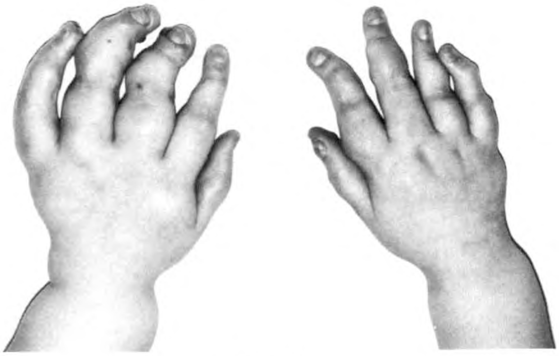

FIG. 2.
Hands, age 13 years 4 months.

Hypertrophy of the bones and soft tissues of the left leg was apparent on the initial radiographs and subsequent hypertrophy of the left lower and upper limbs occurred. He has required several orthopaedic operations and trimming of haemangiomas on the left elbow and hand (Fig. 3) to maintain function and cosmesis, and he requires a surgical boot for his hypertrophied left foot. His height at age 13 years and 4 months was 120 cm. He is intellectually normal and his biochemistry, including mucopolysaccharide estimation, is normal.

Radiological findings

Initial radiographs at age 3 months showed metaphyseal irregularity of all the long bones, including those of the hands and feet, which were flared and cupped with associated lucent areas divided by septa. The left upper and lower limbs were affected more than the right (Fig. 4).

Early irregularity of the pelvic ala and mild platyspondyly were apparent at the same age (Figs. 5A–B). At age 19 months, further disturbance of ossification was seen in the pelvis and upper femora (Fig. 6). At 3 years, expansion of the tarsal bones and early soft tissue calcification were seen (Fig. 7).

Further radiographs at 7 years showed marked metaphyseal irregularity and widespread soft-tissue calcification (Figs. 8A–C). A chest radiograph at that time showed short, anteriorly-flared ribs. Further scalloping of the pelvic ala and disturbance of ossification of the vertebrae had occurred.

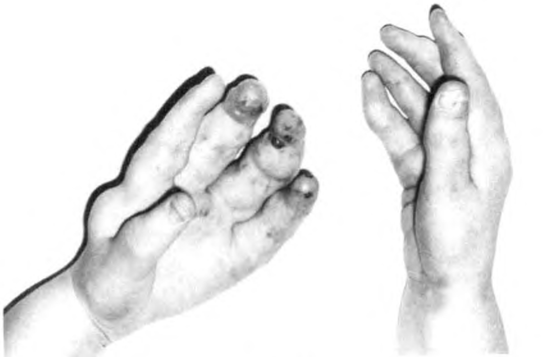

FIG. 3.
Hands: hypertrophy and haemangiomas of the fingers.

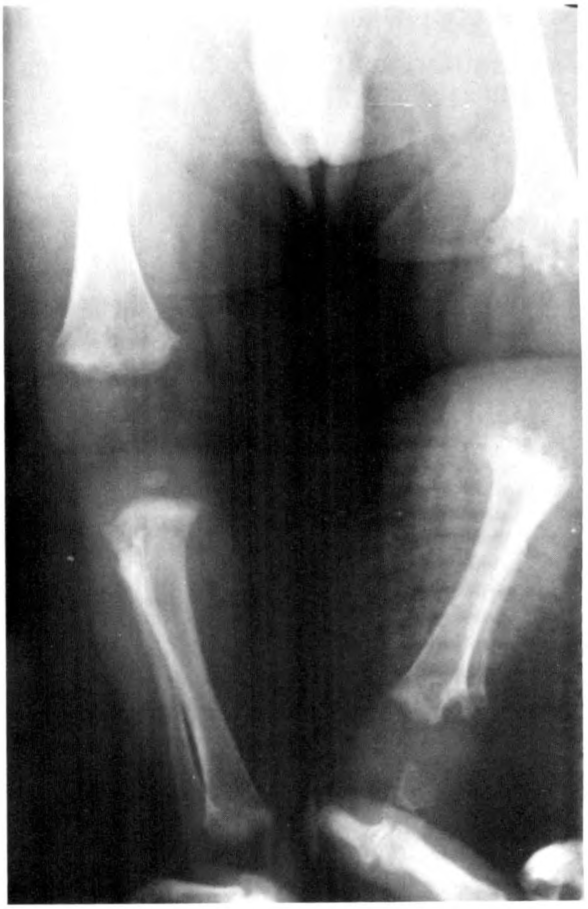

FIG. 4.
Age 3 months.
The lower limbs.

At 14 years, the deformity of the long bones and ribs was very marked (Fig. 9). A radionuclide bone scan was performed because the patient complained of pain over the left elbow. This showed bizarre uptake throughout the skeleton (Figs. 10).

DISCUSSION

Spranger et al (1978) classified the enchondromatoses into six groups: (i) Ollier's disease, (ii) Maffucci's syndrome, (iii) metachondromatosis, (iv) spondyloenchondrodysplasia, (v) enchondromatosis with irregular vertebral lesions and (vi) generalised enchondromatosis.

Our case has some features of all the categories in Spranger's classification except metachondromatosis. It most closely resembles categories (v) and (vi) but differs from (v) in that the short tubular bones are equally involved with the long tubular and flat bones, and from (vi) by the presence of severe disturbance of vertebral ossification rather than mild platyspondyly, and by the absence of skull deformity.

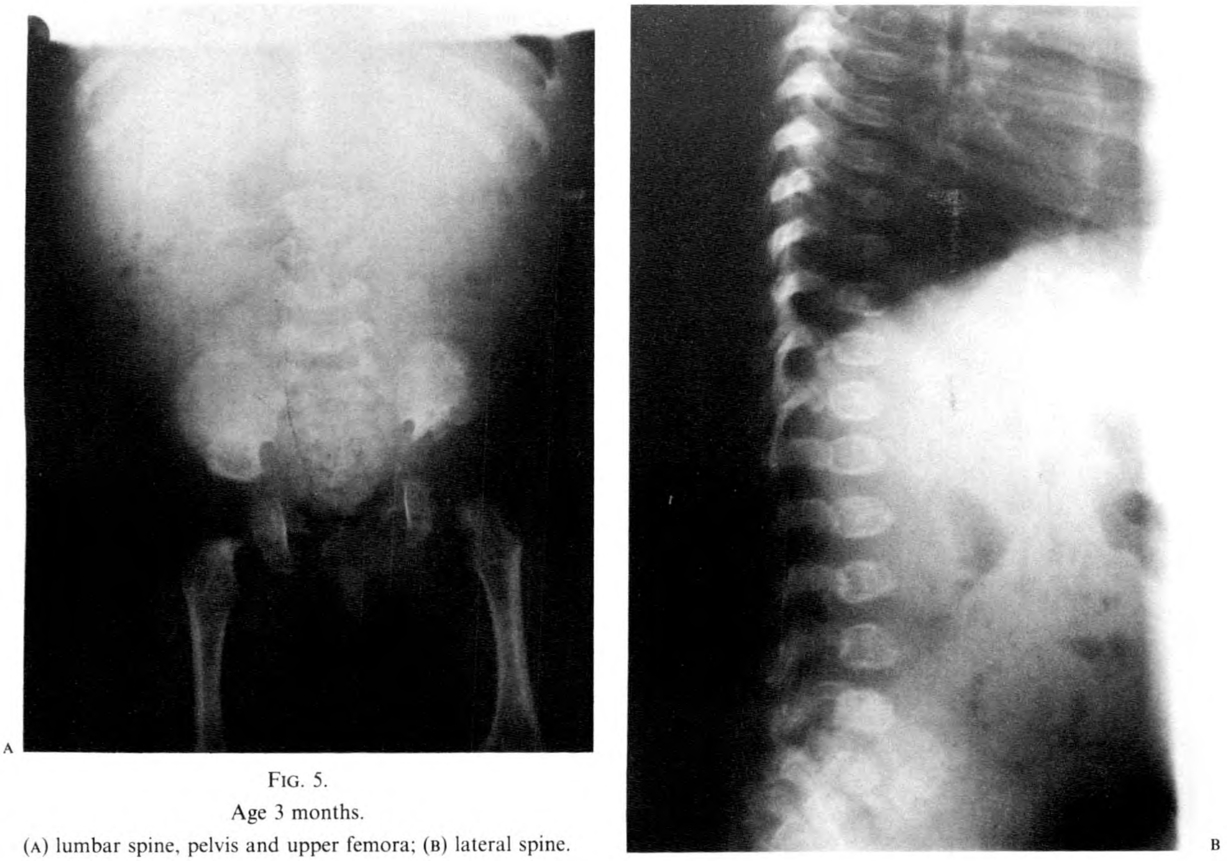

FIG. 5.
Age 3 months.
(A) lumbar spine, pelvis and upper femora; (B) lateral spine.

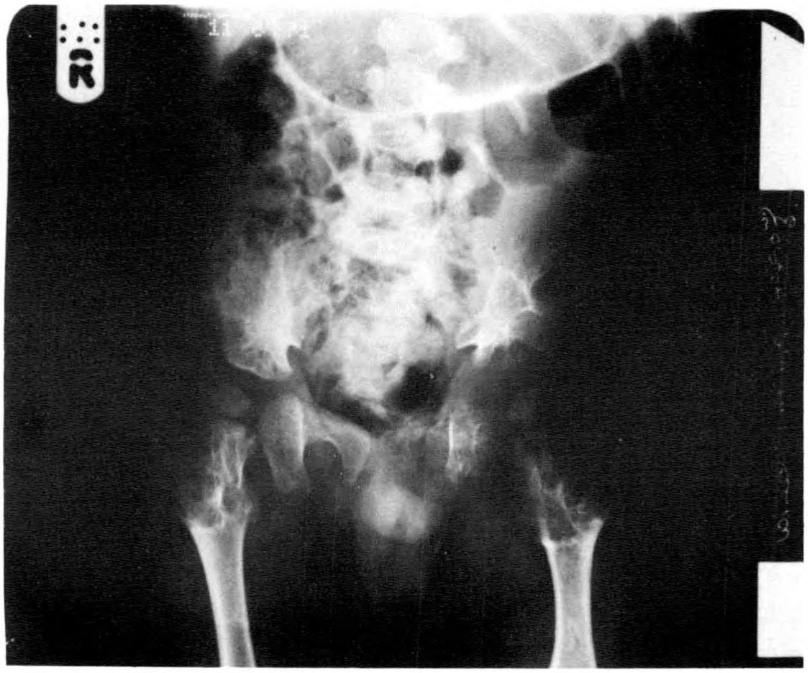

FIG. 6.
Age 19 months. Pelvis and upper femora.

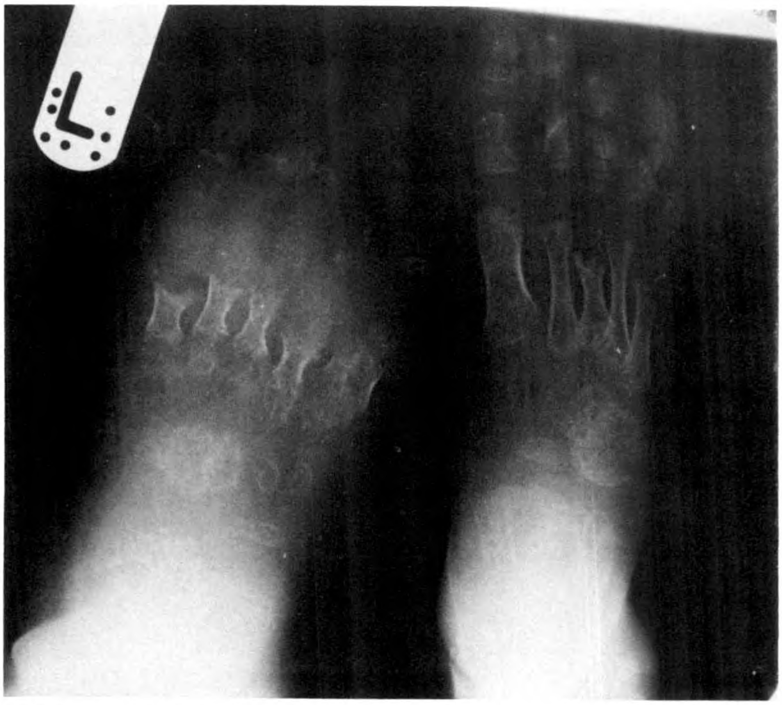

FIG. 7.
Left.
Age 3 years. Both feet.

FIG. 8.
Below.
Age 7 years.
(A) left humerus.
(B) left forearm.

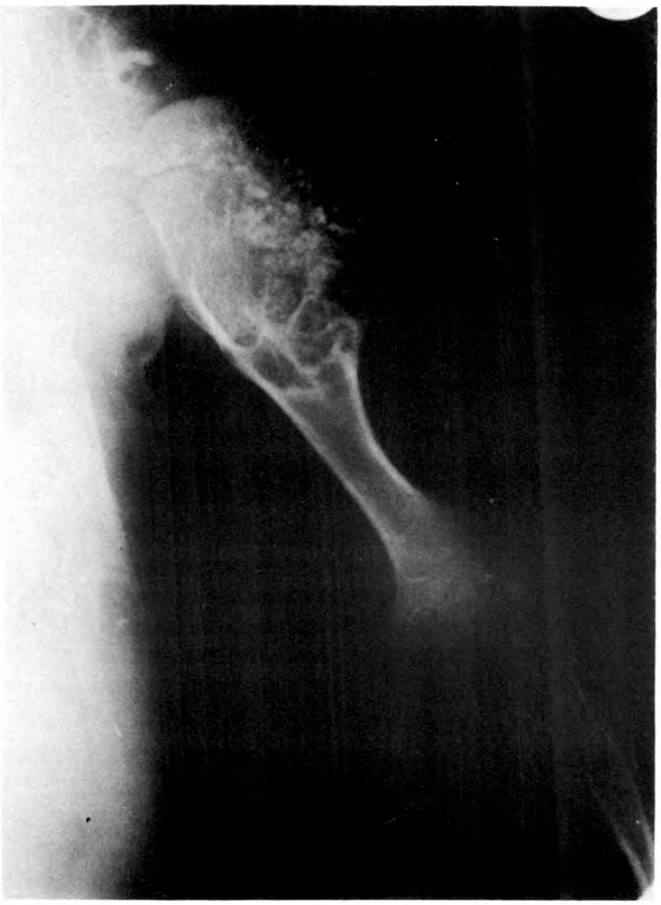

FIG. 8A.

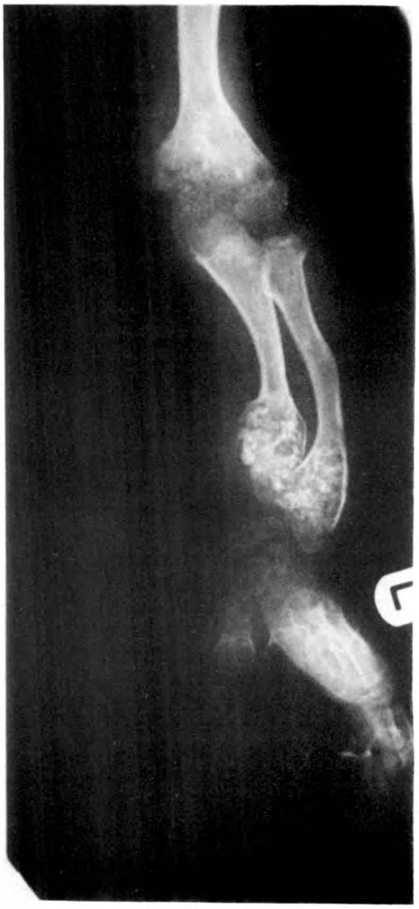

FIG. 8B.

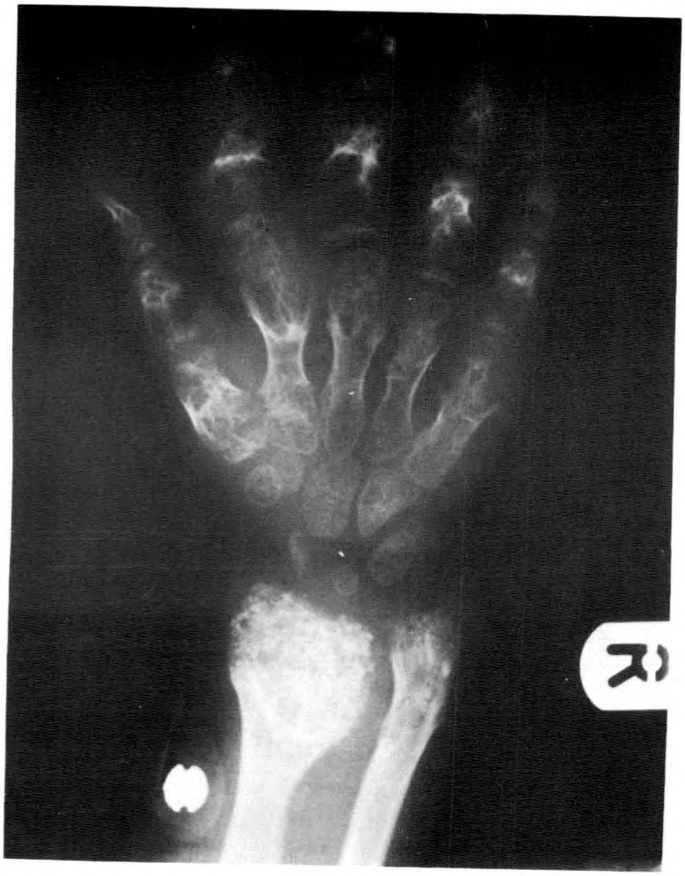

FIG. 8.
(C) Right wrist and hand.

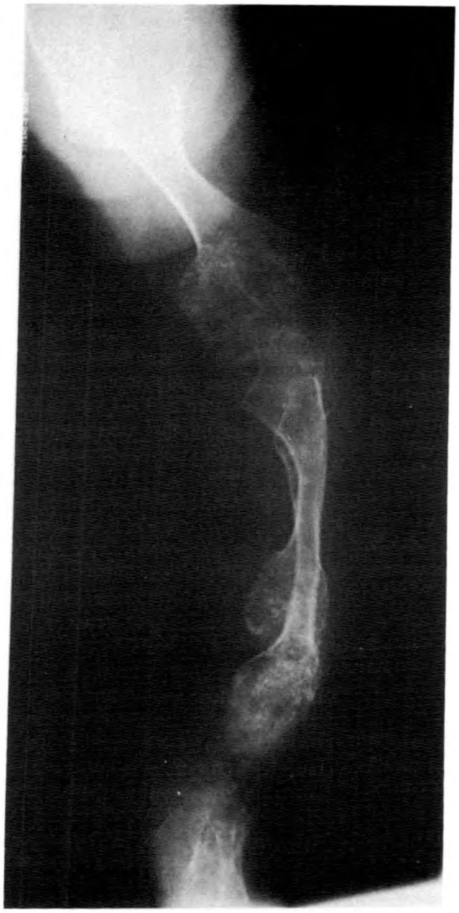

FIG. 9.
Left elbow and forearm.

This may represent a further category in the classification of the enchondromatoses.

Kaibara et al (1982) reported the association of generalised enchondromatosis with haemangiomas and soft-tissue calcifications. Van Creveld et al (1971) also noted haemangiomas in one case of metaphyseal chondrodysplasia calcificans (their Case 2). The same combination in this patient suggests that the association is more than coincidental.

Hemihypertrophy has not previously been described, though hypertrophy can be noted in the radiographs published by van Creveld et al (1971): of the right foot in Case 1, and of the left lower limb in Case 2.

Causes of hemihypertrophy encountered in paediatric practice include fibrous dysplasia, neurofibromatosis, congenital hemihypertrophy and Beckwith-Wiedemann syndrome. There are no features in this case to suggest that another disease is responsible.

In view of the increased incidence of sarcomatous change in patients with Maffucci's syndrome, reported as 23% (Lewis et al, 1973), the outlook for this patient is uncertain. The bizarre changes already present both on radiographs and radionuclide bone scan will make the diagnosis of malignancy very difficult.

He is already limited by his physical deformity and the psychological effects of his disability will become more apparent as he grows older.

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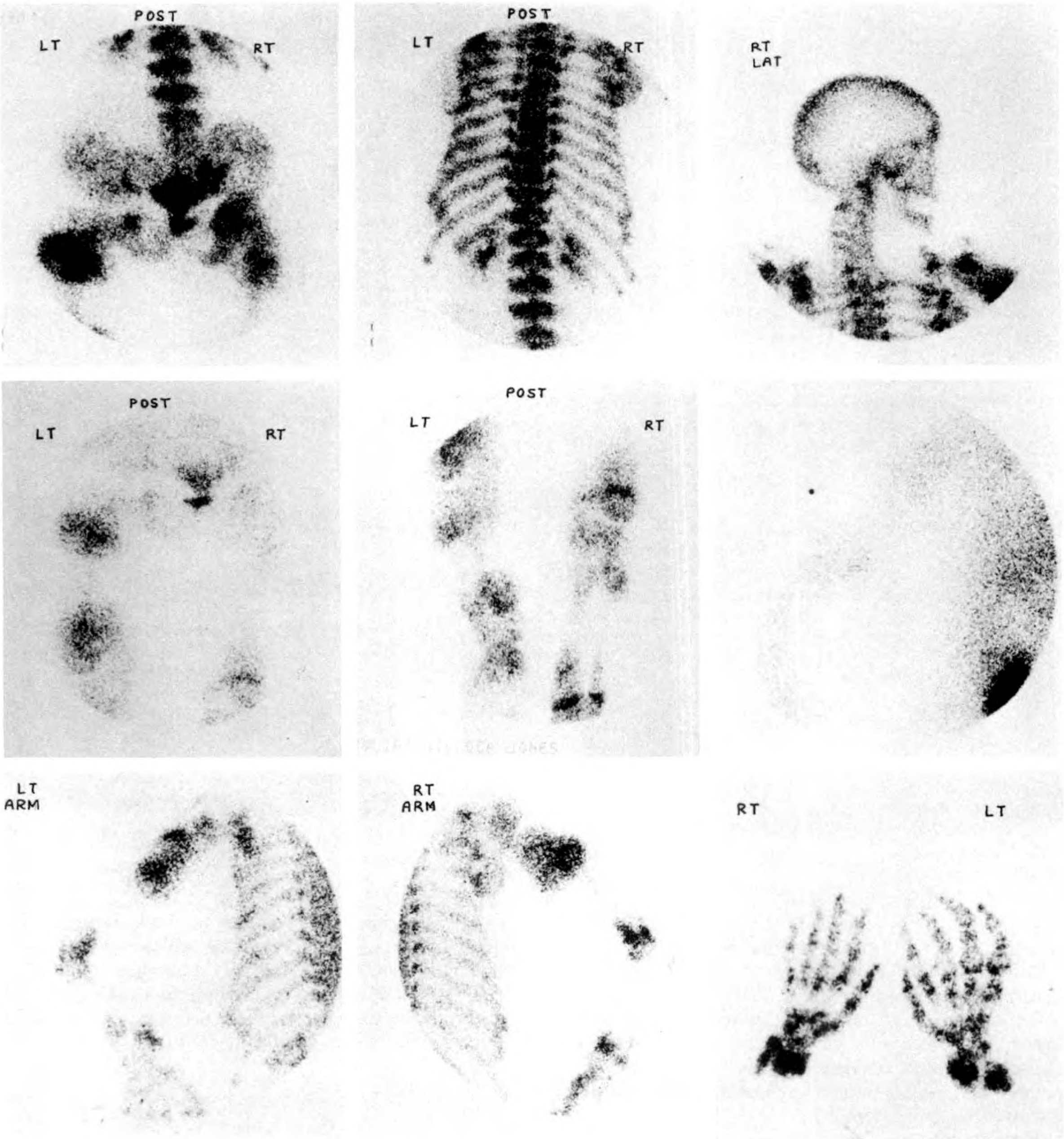

FIG. 10.
Age 14 years. Radionuclide bone scan.

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Hypertrophic osteoarthropathy in a young child with congenital cyanotic heart disease

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Hypertrophic osteoarthropathy in patients with congenital cyanotic heart diseases is extremely rare (Caffey, 1978; Trever, 1958). Of the few cases reported in the world literature, the youngest in which such changes have been seen in congenital cyanotic heart disease is 3½ years (Singh et al, 1972). We present a case of congenital cyanotic heart disease, showing gross changes in all long bones at the age of 2 years.

CASE REPORT

A 2-year-old girl was admitted to Nehru Hospital with low to moderate fever of a month's duration. For about a fortnight preceding admission, she had been complaining of pain in all limbs and particularly in the knee, ankle and elbow joints, severe enough to confine her to bed. Cyanotic congenital heart disease had been diagnosed at the age of 1 year. Recurrent cyanotic spells had necessitated hospitalisation on three earlier occasions and oral propranolol had been prescribed.

Examination revealed a stunted child with cyanosis and grade III clubbing of digits. There was no objective evidence of joint inflammation but she resented movement of her limbs. Clinical examination including electrocardiogram and chest radiograph were consistent with a right to left shunt with a decreased pulmonary blood flow (Fig. 1). Echocardiogram showed transposition of the great vessels with a large atrial septal defect and pulmonary stenosis.

Repeated culture of blood and urine were sterile, but the fever persisted with no apparent localisation. Treatment with cloxacillin and gentamicin for culture-negative bacterial endocarditis was initiated. She became afebrile within a week and therapy was continued for a total duration of 4 weeks. Towards the end of this period she contracted measles and was subsequently discharged. A skeletal survey carried out for her bone and joint pains showed diffuse, marked periostitis in all the long bones (Fig. 2,3). No changes were seen in the metacarpals or metatarsals.

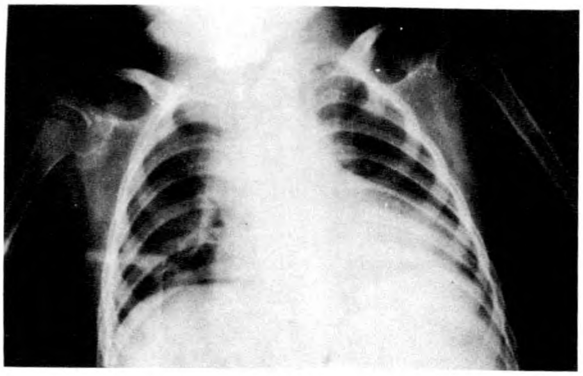

FIG. 1.

Chest radiograph, AP view, showing mild cardiomegaly and bronchopneumonia.

DISCUSSION

Hypertrophic osteoarthropathy (HOA) occurs in lung cancer, mesothelioma and bronchiectasis (Christian, 1979). Trever (1958) quoted Taussig who reported that only three cases of HOA were seen in 3000 patients with congenital cyanotic heart disease. In a study conducted in patients over 6 years old, 10 out of 32 with congenital cyanotic heart disease had HOA, the

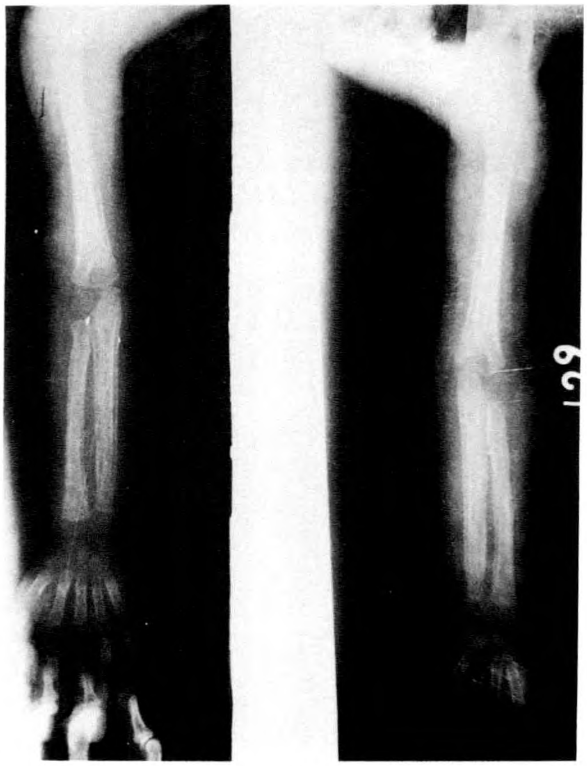

FIG. 2.

Radiograph of both upper limbs showing diffuse periostitis.

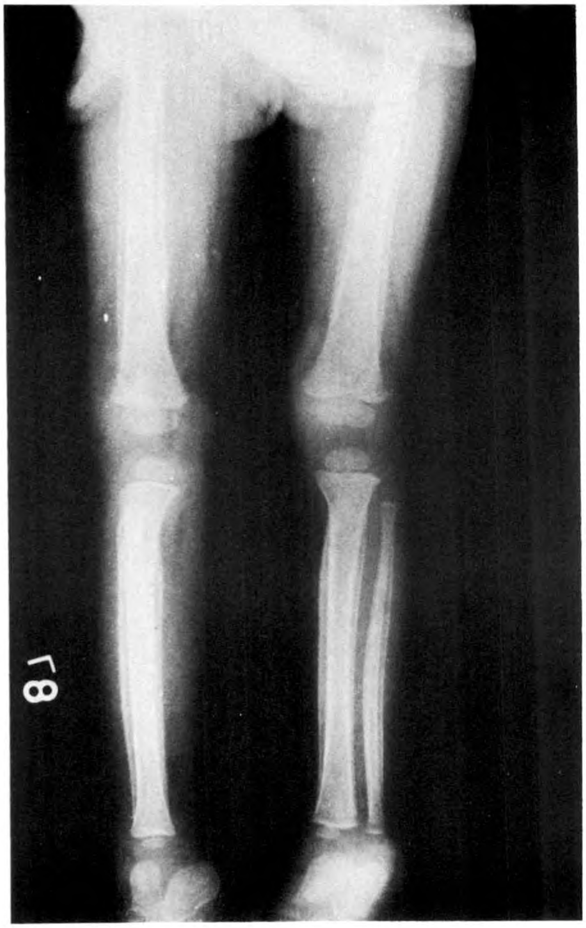

FIG. 3.

Radiograph of both lower limbs showing diffuse periostitis.

youngest being 10 years old (Martinez-Lavin et al, 1982). Another study showed the occurrence of HOA in only four out of 25 patients with congenital cyanotic heart disease, the lowest age being $3\frac{1}{2}$ years (Singh et al, 1972). The development of hypertrophic osteoarthropathy is related to the degree of bypass of the lung. This is consistent with the concept that hypertrophic osteoarthropathy results from mediators in the systemic venous circulation that escape inactivation in the pulmonary capillary bed.

HOA in congenital cyanotic heart disease at the age of $3\frac{1}{2}$ years (Singh et al, 1972) and in our patient at the age of two clearly indicates that the extensive bone involvement need not be related to the duration of cyanosis, but may be closely related to the degree of cardiac decompensation.

Further knowledge of the pattern of bone involvement and its permanence or otherwise can be obtained only if the skeleton is included in routine examination.

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Case of the month

Pain in the hand in the presence of mediastinal mass

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(*Received September 1984*)

A 75-year-old retired electrician presented with gradual onset of pain and numbness in the ring and little fingers of the right hand over a 6 month period. He had also noticed stiffness of the shoulders, more marked on the right. There was no past medical history of note; he had been a smoker since the age of 18.

On examination he had restricted movement of both shoulders but no muscular wasting or weakness. Hyperaesthesia of the palmar aspects of the right ring and little fingers was elicited. Blood pressure was 160/90. Investigations revealed an ESR of 40 mm/h. A full blood count was normal. On the PA chest radiograph (Fig. 1) there was a right upper mediastinal mass. The lateral radiograph showed anterior displacement of the trachea (Fig. 2); a barium swallow was therefore performed which shows a posterior impression on the oesophagogram at the level of the aortic arch (Fig. 3).

PROBLEM

The patient's symptoms suggest a lesion involving the right brachial plexus; the right superior mediastinal mass could thus represent either local lymphadenopathy from a tumour involving the brachial plexus, or possibly direct spread of a superior mediastinal tumour into the neck. However, a posterior indentation of the oesophagus at the level of the aortic arch on the lateral or left anterior oblique view is suggestive of aortic arch anomaly, of which the commonest is aberrant right subclavian artery, with an incidence of 0.5% in the general population. Such vascular anomalies do not normally produce a mass bulging into the right hemithorax. What investigation would you request next?

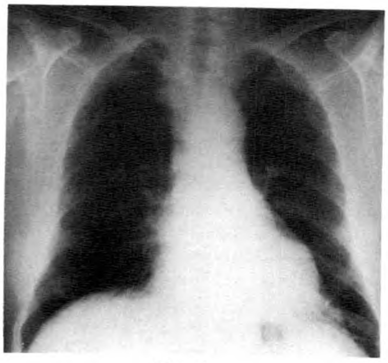

FIG. 1.

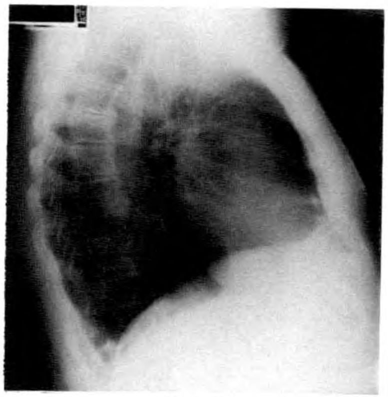

FIG. 2.

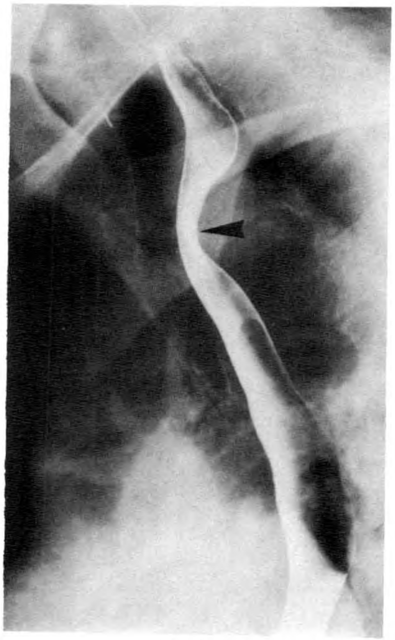

FIG. 3.

Computed tomography with intravenous infusion of 60 ml meglumine diatrizoate 65% (Urografin 310M) at 4 ml/s was undertaken. The slice thickness was 8 mm, in contiguous sections. Scan time 5 s.

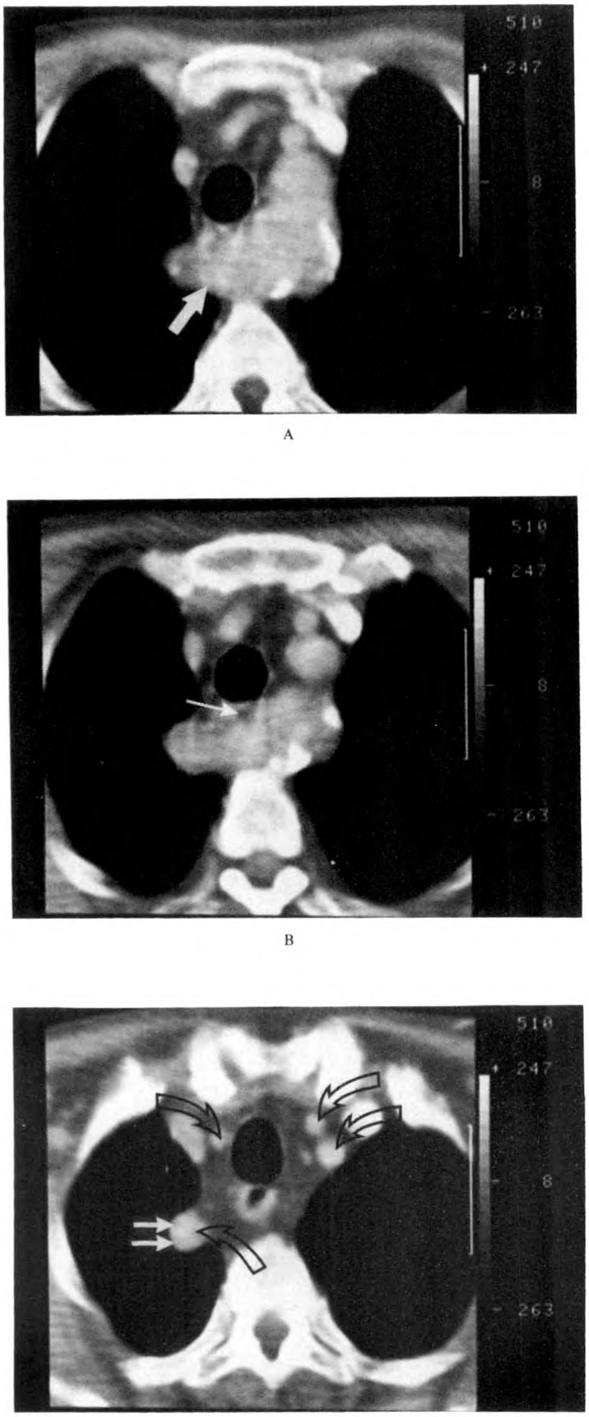

FIG. 4.

This study demonstrates an aberrant right subclavian artery (A, thick arrow) arising as the last branch of the aortic arch. It is wider proximally than distally as the first part represents the dorsal portion of the right 4th branchial arch. The vessel passes behind the oesophagus (B, thin arrow) before turning superiorly to ascend in the right paramediastinal space (Klinkhamer, 1966). It lies more posterior than the normal position of the right subclavian artery; this is one of the CT features of this anomaly (McLoughlin et al, 1981). The aberrant artery bulges laterally into the right hemithorax (C, double arrow), thus explaining the plain film findings. This is an unusual feature and in this case it is probably due to atherosclerotic tortuosity. A similar plain film appearance is caused by aneurysmal dilatation of an anomalous right subclavian artery although this is a rare disorder, only 11 cases being described in the literature (Lupetin, 1984).

Computed tomography has been used to diagnose a variety of aortic arch anomalies including right-sided aortic arch associated with an aberrant left subclavian artery. The appearances are not a mirror image of the findings in this case as the aortic arch undergoes torsion and lies not only to the right but also posterior to the trachea. In either case the "4-artery sign" should be present. All four branches of the aortic arch arise separately, and one can therefore identify four contrast-filled arteries in the superior mediastinum (C, open curved arrows).

CT was useful in this case because it allowed a superior mediastinal mass such as reduplication or bronchogenic cyst, lymphadenopathy due to carcinoma of the bronchus or stomach or as a result of lymphoma, and neurogenic tumours to be confidently excluded.

The salient CT features are the retro-oesophageal course of the aberrant vessel, its relatively posterior position in the superior mediastinum and the "4-artery sign". The cause of the patient's symptoms is still unknown.

ACKNOWLEDGMENTS

We wish to thank Dr. J. M. B. Hughes for permission to report this case, and Diana Spencer who performed the CT investigation.

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1986, *The British Journal of Radiology*, 59, 79–80 JANUARY 1986

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

Hexabrix and gallbladder visualisation

THE EDITOR—SIR,

Gillespie et al (1985) have documented an important and potentially misleading phenomenon We have seen two adult cases of gallbladder opacification at approximately 24 h following intravenous urography in one and arteriography in the other and can confirm that it is not confined to paediatric practice.

The authors correctly point out that the protein-binding capacity of Hexabrix is close to that of iothalamate and cannot, therefore, be the important factor Indeed, it is now recognised that, while protein binding may help retain a drug in the intravascular space and inhibit its filtration by renal glomeruli, it does not itself lead to hepatic excretion (Knoefel, 1971) Several studies have shown that serum protein binding may impede hepatic uptake (Grauz & Schmidt 1971, Barnhart & Clarenburg, 1973; Song et al, 1976), the mechanisms of which remain obscure There is, however, evidence of receptors on the sinusoidal liver cell membrane or in its cytoplasm which may determine preferential uptake and excretion (Cornelius et al, 1967) In the context of receptors, it is illuminating to compare the structure of sodium meglumine ioxaglate (Hexabrix, May & Baker Ltd) with that of meglumine ioglycamide (Biligram, Schering) (Fig. 1). They are closely similar and may share a hepatocyte receptor However, further consideration of the structures inevitably takes us back to protein binding since the only major difference between them is that the true biliary agent has unsubstituted positions on each benzene ring. It is this which presumably makes it a much better biliary agent than Hexabrix, but it is also this which enormously increases its protein-binding capacity (Lang & Lasser, 1967) Clearly, there are still questions about the hepatic uptake and excretion of contrast agents, but these will probably remain unanswered because the requirements for biliary directed contrast agents has markedly declined.

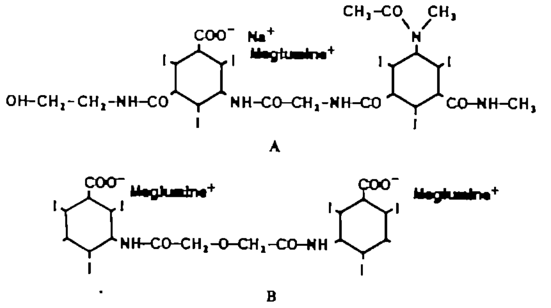

FIG. 1.

Structures of (A) Hexabrix and (B) Biligram.

Yours, etc.,
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Biliary tract opacification following intravenous Hexabrix: a normal phenomenon detectable by computed tomography

THE EDITOR—SIR,

By selecting patients referred for intravenous urography and by performing the urograms with either 50 ml of Hexabrix 320 (May & Baker Ltd) or 50 ml Urografin 370 (Schering AG) we have demonstrated that:

((a) 10 out of 10 patients (mean age 47 years) given Hexabrix showed opacification of the gallbladder and common bile-duct on CT images acquired at a mean time interval of 82 min from the injection, and
(b) none of seven patients (mean age 52 years) given Urografin exhibited a similar effect on CT images acquired after a mean interval of 78 min.

None of the patients in the Hexabrix group was in renal failure and none had evidence of acute renal tract obstruction, factors known to favour biliary excretion of urographic contrast media. None of the patients in either group had known hepatic impairment

These results concur with the observations of Gillespie et al (1985) of a much higher incidence of gallbladder opacification on abdominal radiographs obtained 24 h after Hexabrix than would be expected 24 h after diatrizoates

The most likely explanation for the higher biliary concentration of Hexabrix is, as suggested by Owman and Olin (1978), that Hexabrix is actively excreted in the bile, whereas the diatrizoates are passively eliminated Contrary to Gillespie et al, our interpretation of Owman and Olin's paper is that

1986, *The British Journal of Radiology*, *59*, 80–82

there is no difference in the choleretic effects of Hexabrix and diatrizoates.

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Indium-111 radioactivity in breast milk

The Editor—Sir,

The use of ^{111}In-labelled white blood cells instead of ^{67}Ga citrate in radionuclide imaging is increasing. We have recently measured the concentration of ^{111}In in breast milk following the administration of ^{111}In white cells to a lactating woman. The labelling was carried out using the Tropolone method. The activity injected was 12 MBq (0.32 mCi). Milk was expressed 6 h and 20 h after the injection of the radiopharmaceutical (220 ml and 170 ml, respectively). The total radioactivity was measured and corrected to the times at which the samples were obtained. The results were calculated as concentration per activity originally administered.

The results obtained, 0.09 Bq/ml and 0.20 Bq/ml per MBq injected (0.09 nCi/ml and 0.20 nCi/ml per mCi) at 6 h and 20 h indicate that breast feeding is safe if this radiopharmaceutical is used in lactating women. Assuming five feeds of 100 ml each, the daily activity ingested by the infant would be 100 Bq per MBq (100 nCi per mCi) given to the mother or a few kBq (0.1 μCi) per investigation. The annual limit on intake of ^{111}In for workers is 200 MBq (5.4 mCi) (ICRP, 1980) and for members of the public is 20 MBq (0.54 mCi); the latter value when adjusted for the weight of an infant is 1 MBq (27 μCi).

When ^{67}Ga or ^{99}Tc^{m} radiopharmaceuticals are used for imaging, the radioactivity in breast milk is considerably higher than the values measured for ^{111}In and the suspension of breast feeding for various periods has been advised (Greener et al, 1983; HPA 1984). The subject has recently been reviewed (Coakley & Mountford, 1985).

Table I shows some published concentrations of radionuclides in breast milk.

TABLE I

Radiopharmaceuticals in breast milk

Radiopharmaceutical	Time (h)	Concentration Bq/ml per MBq (nCi/ml per mCi) injected	Reference
^{111}In white cells	6	0.09	Present work
	20	0.20	
^{113}In^{m} chelate	2	0.25	Pullar & Hartkamp, 1977
^{67}Ga citrate	72	50	Tobin & Schneider, 1976
	88	46	Greener et al, 1983
^{99}Tc^{m} pertechnetate	2	51	Wyburn, 1973
	10	8.3	
	22	0.3	

Yours, etc.,
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Clinically derived dose–effect relationship for hyperthermia given in combination with low-dose radiotherapy

The Editor—Sir,

The excellent paper by van der Zee et al (1985) raises an interesting issue in its discussion section "It is very encouraging that it has proven possible to demonstrate a clinically derived dose-effect relationship for hyperthermia. It is surprising however that this relationship was found for the mean temperature achieved in the tumour and not for any of the equivalent times at a reference temperature of 43°C." There are two, if not more, simple explanations for this. Firstly, this clinical material is spontaneous cancer, whereas the experimental data are all derived from transplanted animal cancer. Secondly, the hyperthermia was induced using electromagnetic radiation. Eight years ago it was pointed out that there was a different human clinical response for any given dose of radiation, depending upon whether the hyperthermia was created by simple heating or induced by electromagnetic radiation (Holt, 1977).

A comparison of radiosensitising effects of the same dose of radiation combined with the same temperature, induced by either modality, leads to the incontrovertible conclusions that electromagnetic radiation produces hyperthermia but also produces a non-thermic radiosensitisation. These observations were the stimulus for Professor W. T. Joines' work which shows the differences in electrical conductivity between cancer and the normal tissue (Joines, 1977). The electromagnetic radiation energy deposited in cancer and normal tissue is dependent upon its electrical impedance, *i.e.*, conductivity and other electrical parameters. Joines has reported that selective deposition of energy occurs in cancer, relative to normal tissue, and that this ratio may be as high as 4 : 1. It is, therefore, not in any way surprising that the clinically derived dose-effect relationship for RF hyperthermia should relate to the mean temperature.

It is my clinical experience that the radiosensitising effect of an applied RF field is linearly related to the amount of electromagnetic energy absorbed. On the other hand, hyperthermia experiments (non-RF generated) show a very rapidly increasing effect (direct cell kill) as the temperature rises above 42°C. Hence, for simple heat therapy it would be expected that the maximum or peak temperature reached would be more relevant.

As I have pointed out at international meetings and in this Journal (Holt, 1980), it is clinically obvious that the radiosensitivity increase is unrelated to the peak temperature generated in the cancer by electromagnetic radiation. To establish hyperthermic radiosensitisation experimentally requires simple heating, because when using electromagnetic radiation heating there is a radiosensitising effect due to hyperthermia and a radiosensitising effect which is unrelated to a rise in temperature. Experiments which reveal these two separate effects have been pioneered by Johnson et al (1979).

Yours, etc.,
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(*Author's reply*)

THE EDITOR—SIR,

We appreciate the attention paid by Dr. Holt to the results of our clinical study. Dr. Holt's letter deals with the surprise expressed in our paper that the effect of the mean tumour temperature achieved could be discerned in the response rate, but that this did not hold for the equivalent time at a reference temperature of 43°C. Dr Holt is *not* surprised, and offers at least two explanations for this phenomenon; firstly, the clinical material represents spontaneous cancer and, secondly, the hyperthermia was generated with electromagnetic radiation.

We are familiar with some of Dr. Holt's ideas and observations but prefer to adopt a different point of view on some of the items raised in his letter.

With reference to the question as to whether human cancer differs from experimental tumours in rodents, we agree with Dr. Holt that there will be many differences, *e.g.*, with respect to the site of the tumour, its relative volume, proliferation rate, degree of differentiation, and vascularisation. However, even taking all these factors into account, the response rates of experimental tumours and human cancers to a combination of heat and radiation show striking similarities rather than differences (Hahn, 1982b).

The second explanation offered by Dr Holt deals with the possibility that electromagnetic radiation may have a non-thermal radiosensitising effect, in addition to the hyperthermic effect. Although one should always keep an open mind with respect to unexpected effects, our interpretation of the available experimental evidence is that non-thermal radiosensitisation and cytotoxicity, if they exist at all, are of little importance in comparison with the hyperthermic effects. This holds for *in vitro* (Robinson et al, 1981, Sapareto, et al, 1982, Hahn, 1982a) as well as *in vivo* systems (Marmor et al, 1977). It is, rather, the thermal gradient in tumours which has been shown to influence the degree of hyperthermic radiosensitisation (Gibbs et al, 1981).

It has been demonstrated in many experimental studies that tumour cell kill (enhancement) depends on both the level of temperature achieved *and* the duration of treatment (Field & Morris, 1983). It is difficult to verify this effect in clinical studies because it is not, as yet, possible to obtain controlled homogeneous tumour heating.

Our impression, after treating over 180 patients, is that the tumour temperatures achieved bear little relation to the level of power input. The temperature achieved depends not only on electromagnetic absorption characteristics but also, to a considerable extent, on tumour blood-flow. If non-thermal effects were to play an important role in cytotoxicity and radiosensitisation following electromagnetic heating, the finding of a dose-effect relationship for mean tumour temperature (unrelated to power input) would be even more surprising.

We would not presume to call the observed clinical results "radiosensitisation", as there was no comparison with a control group of patients treated with radiotherapy alone. In a clinical study of this nature the additional effects of hyperthermia can not be separated from a possible radiosensitising effect. Furthermore, radiosensitisation may not even occur when the time interval between radiotherapy and the start of hyperthermia treatment is, as it was in our series, as much as 40 min (Overgaard, 1985).

Dr. Holt is fortunate in that he feels able to draw so many definitive conclusions from a limited study of 11 patients in whom no measurements of individual temperatures were made (Holt, 1980). With respect to our somewhat larger study, such a degree of personal conviction is precluded by the wide range of variation in the data obtained and the sobering effect of the imposition of statistical criteria to establish the significance of those results.

Correspondence

In view of the absence of conclusive evidence to support the existence of non-thermal effects we retain our hypothesis that the applied heat dose, which is dependent upon both the temperature obtained and the exposure time, is the critical parameter. In this case extensive thermometry is required to ensure that the patient receives an effective adjunct treatment to radiotherapy.

Yours, etc.,
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The absence of tissue specificity in MRI using *in vivo* T_1 or T_2 determination: true biological variation or technical artefact?

THE EDITOR—SIR,

The discovery by Damadian (1971) that malignant tissue measured *in vitro* has a higher T_1 than normal tissue acted as the stimulus for the development of NMR imaging techniques. In the beginning it was hoped that *in vivo* measurements of relaxation parameters may uniquely identify different tissues or the same tissue in different pathological states, perhaps enabling the differentiation between normal, benign or malignant tissue. However, by the time commercial magnetic resonance imaging (MRI) systems became available in about 1982, the emphasis in MRI system design was generally not on precise or accurate *in vivo* T_1 or T_2 determination but rather higher resolution image production, the images being T_1 or T_2 weighted. It is generally accepted now that neither T_1 nor T_2 are disease-specific, there being too great an overlap for diagnostic purposes.

We feel that this conclusion may be erroneous. The spread of T_1 or T_2 values from a particular tissue may not be due solely to the biological variation but instead may be significantly expanded due to technical errors in their calculation. There are a number of possible sources of error in the *in vivo* relaxation parameter determination.

(a) The calculation of *in vivo* T_1 from a saturation recovery and an inversion recovery pulse sequence will have an error if there is not efficient inversion in the latter sequence. This will occur in all imaging systems when a spatially selective 180° pulse is used or when there is significant radiofrequency inhomogeneity across the image plane. An exception is the system which uses an adiabatic fast passage RF pulse (Edelstein et al, 1980), which efficiently inverts all the nuclei.

(b) Some two-point methods of relaxation parameter calculation are known to be imprecise; for example, two saturation-recovery or two spin-echo sequences with different TR or two inversion-recovery sequences with different TI to calculate T_1 and two spin-echo sequences with different TE to calculate T_2. More precise estimations using such sequences require a larger number of points each with a different TI or TE value to be used.

(c) The spin–spin and spin–lattice relaxation processes may not be characterised by a single exponential.

(d) The width of the tomographic sections used in MRI, particularly when values of T_1 or T_2 are being calculated, can be as thick as 20 mm. As a consequence there can be a significant partial volume effect. The partial volume effect can produce a considerably reduced estimate of the T_1 or T_2 in a pathological lesion which has a higher value than surrounding normal tissues unless the lesion was extremely large. Much thinner section widths must, therefore, be used for accurate *in vivo* T_1 or T_2 determination; the thickness of the section should be about half the diameter of any tissue under investigation and care must be taken to position the section through the centre of the tissue.

(e) It is recognised that cardiac and respiratory movement degrade the resolution of images; this can be avoided by the use of gating techniques. However, not only does it degrade image resolution, it will also produce an error in the calculation of T_1 or T_2 if the tissue is moving.

(f) There can be an error introduced due to subjective operator variation in the choice of region for T_1 or T_2 calculation.

Experience has shown that, as the techniques of *in vivo* T_1 and T_2 determination are improved, so the spread in their values from a particular type of tissue is reduced. Only when the technical errors of T_1 and T_2 measurement are eliminated can we hope to draw any firm conclusions concerning their specificity and consequent clinical use.

Correspondence

We would recognise that in many MRI systems it is not possible to eliminate all the sources of technical error, particularly as there is often limited time available for patient investigation. In the centres which adopt a pragmatic approach to T_1 and T_2 calculation and are investigating its use in the clinical environment, knowing that, for technical reasons, the values obtained may not be entirely accurate, we would suggest that such quantitative values should be defined as T_1** and T_2**. The term T_1 and T_2 would be reserved for what is believed to be true biological relaxation times.

Yours, etc.,
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Radioprotection by ascorbate *in vitro*: temperature-dependent uptake

THE EDITOR—SIR,

The role of glutathione in radioprotection has been much investigated, but relatively little attention has been paid to ascorbate, which is present at high concentrations in human tumours (Kakar & Wilson, 1974; Moriarty et al, 1977). Both glutathione and ascorbate can act as H-atom donors, although ascorbate is more efficient in electron transfer reactions, and both these reactions may be important in DNA repair processes (Redpath & Willson, 1973; O'Neill, 1983; Willson, 1983). There have been some reports in the literature of radioprotection by ascorbate *in vitro* (Redpath & Willson 1973; O'Connor et al, 1977; Baverstock, 1979) but other workers have found no effect of ascorbate on radiosensitisation by misonidazole (Koch et al, 1979).

As a part of an investigation into the radioprotective role of ascorbate *in vitro*, we have measured the uptake of ascorbate by V79 379A Chinese hamster cells incubated in Eagles' minimum essential medium +10% fetal calf serum at various temperatures. Figure 1 shows the concentration of ascorbate in cells plotted against time of incubation under N_2 at 4°C, 21.5°C and 36°C. The point we would wish to emphasise is the marked temperature-dependence and slow time course of the uptake, with essentially no uptake at 4°C, and intracellular concentrations increasing for several hours at the higher temperatures. In some radiobiological experiments the pre-irradiation incubations are carried out at 4°C in order to reduce toxicity. If the agent of interest is actively transported, or is taken up slowly, both of which appear to apply to ascorbate, a lack of effect could arise from poor intracellular uptake rather than inactivity *per se*. Thus, Koch et al (1979) showed that ascorbate at 5 mM had no effect on radiosensitivity when the pre-gassing was carried out at 4°C. We have recently shown that if pre-incubation is at room temperature, then ascorbate can afford significant protection in both control and GSH-depleted cells (Fig. 2). Full details will be published elsewhere. We would, therefore, like to take this opportunity to emphasise the importance of measuring the uptake of any

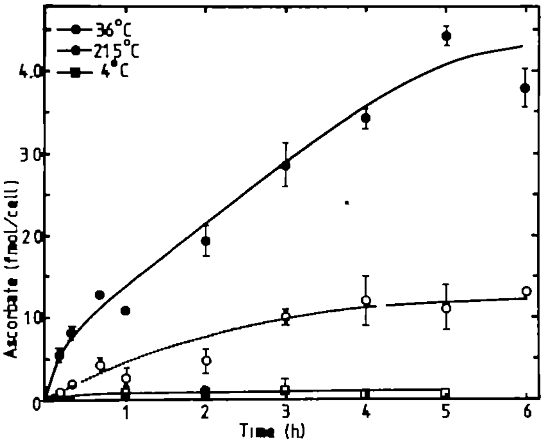

FIG 1.

Temperature-dependence of the uptake of ascorbate by cells incubated with 0.5 mM ascorbate under N_2. Error bars indicate ±SD.

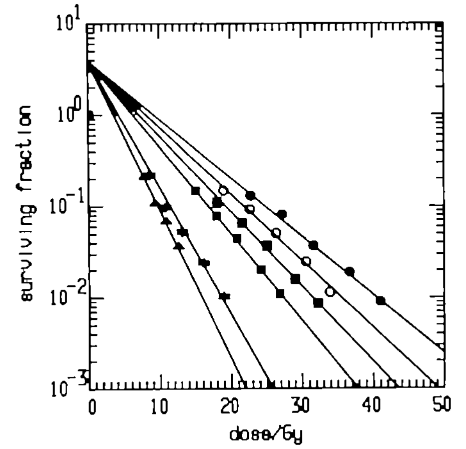

FIG. 2.

Survival curves for cells irradiated under N_2, in the absence or presence of ascorbate. (A) (○) Hypoxic control, (●) 1 mM ascorbate; protection factor (PF) = 1.14. (B) Cells incubated with the inhibitor of glutathione (GSH) biosynthesis buthionine sulphoximine (BSO) (0.1 mM) for 18 h: (□) hypoxic control, (■) 0.2 mM ascorbate; PF = 1.15. (C) GSH depleted cells + misonidazole (0.1 mM): (△) hypoxic control, (✱) 0.2 mM ascorbate; PF = 1.17. In each case, the PF is quoted relative to the paired survival curve in the absence of ascorbate.

compound which is being investigated for its radiobiological activity. Dennis et al (1985) have shown that uptake of radiosensitisers is markedly dependent on chemical properties and factors such as extracellular pH

Yours, etc.,
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Proceedings of The British Institute of Radiology

Radiation oncology—the state of the art

Abstracts of papers presented at the above meeting, which was held at Scientific Societies Lecture Theatre, New Burlington Place, London W1, on Friday, May 17, 1985

Chairman: Professor R. J. Berry

The problem, by Professor R. J. Berry
Planning the treatment, by Mrs P. Hobday
Imaging integration with treatment planning, by Dr. D. V. Ash
The equipment for therapy, by Mr. M. J. Kandes and Dr. D. A. Goer
Dynamic therapy, by Dr. D. B. L. Skeggs
Patient immobilisation, by Miss P. Curtis
Hyperthermia, by Professor Norman M. Bleehen
How do you define treatment success?, by Dr. R. F. Mould
What the radiographer wants, by Mr. S. H. Crookes
What next?, by Mr. I. C. P. Millar

CHAIRMAN'S OPENING REMARKS

In the United Kingdom, malignant disease is responsible for the deaths of one in four of all males and one in five of all females. Despite advances in our understanding of the biology of malignant disease in recent years and the evolution of cytotoxic chemotherapy, radiotherapy is still the major mode of treatment of approximately half of all new cancer patients. Its use is increasing in certain areas such as breast cancer where current evidence suggests that tumour local control can be achieved without mutilating surgery by using cosmetically acceptable modern radiation techniques. This, however, has dramatically changed the workload of the radiotherapy department.

The imaging revolution has brought about a new ability to identify where tumour is and to integrate the planning of radiation therapy to assure the inclusion of all gross tumour and to minimise dose to limiting normal tissues. The advent of modern particle accelerators allows extremely high precision radiotherapy—but at a cost. This meeting is designed to bring together the users of modern radiotherapy equipment—radiation oncologists, physicists, radiographers and the makers in a dialogue about what we want—and what we can afford—for the cost-effective treatment of the patient with malignant disease.

PLANNING THE TREATMENT

Pauline Hobday

IGE Medical Systems

The use of high-energy radiation to treat oncology patients usually involves the development of a treatment plan before irradiation is commenced.

In order to develop a treatment plan, a knowledge of the therapy machine characteristics together with information on the patient anatomy and localisation of the tumour is required. The recent application of CT to radiotherapy has provided a very good tool for localisation of body contour, normal anatomy and tumour. In addition, a new generation of CT-based planning computers has recently emerged, using CT data both qualitatively and quantitatively in the dose calculations.

The aim of radiotherapy planning is to achieve a uniform dose to the target volume whilst avoiding damage to normal structures. In order to realise this aim when planning the treatment, it is necessary to be able to:

perform an accurate calculation of dose;
combine beams, and optimise the dose distribution with beam, weighting, wedges and compensating filters;
visualise and calculate distributions for non co-planar beams, and
visualise the dose distribution throughout the target volume.

The final stage of planning the treatment is the verification of the plan. This may be done using the simulator in combination with a check film on the therapy machine, or perhaps using a beam's eye view as generated by the planning computer to verify coverage of the target volume.

IMAGING INTEGRATION WITH TREATMENT PLANNING

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The application of new imaging techniques, and in particular CT, to tumour localisation has indicated that CT shows that approximately 30% of tumours are incorrectly localised by conventional radiology and clinical examination (Dobbs et al, 1983). As a result of this, radiotherapy treatment plans may fail to include the whole of the target volume within the desired isodose and parts of the tumour may be underdosed by as much as 30–40%. There has been little data so far on the effect that this may have on outcome, but a recent study in bladder cancer has shown a highly significant difference in survival between those patients whose tumours were included within the 90% isodose and those that fell outside (Rothwell, et al, 1985).

The information available from CT should therefore be integrated directly into the planning process so that the improved tumour localisation data can be used both for preparing a plan and setting up the patient. This however requires meticulous attention to the details and reproducibility of patient positioning so that the information from CT is directly transferable to the treatment couch (Ash et al, 1983).

New techniques of 3-D dosimetry using CT reconstruction (Dutreix, 1984) and the use of inhomogeneity corrections allow a much more accurate appreciation of dose within the target volume and within numerous planes outside the main axis of the beam. These improvements in accuracy are however only a link in the planning/treatment chain which is only as strong as its weakest link The ability to position the patient so that the beam hits the target at every treatment fraction is now the main limitation to accuracy, and further attention to patient positioning and immobilisation and to treatment verification is necessary if the advantages of new imaging and planning techniques are to be translated into treatment benefits.

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THE EQUIPMENT FOR THERAPY

Martin J. Kandes and Donald A. Goer

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Radiotherapy must translate a disease diagnosis into a treatment strategy. The treatment strategy must then be accurately planned and delivered in precise accordance with the treatment prescription—reproducibly over a three to six week period. Depending on the tumour location and extent of disease, a variety of beam energies or modalities might be required. Finally, the results of the treatment must be followed and evaluated.

In the 40 years in which linear accelerators have been in use, significant technological advances have been made in all areas of radiotherapeutic management. These improvements have demonstrably resulted in improved survival and reduced morbidity.

This paper describes some of the most recent advances in treatment units; advances which are likely to provide greater flexibility, improved dose delivery techniques, and more cost effective utilisation of the equipment to the radiotherapist.

DYNAMIC THERAPY

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The philosophy of dynamic therapy has been discussed over the last 30 years since T. A Green described the modification of a Marconi 250 kV machine for this intention It was then dismissed as an impractical diversion in radiotherapy, but in spite of this, developmental work continued. The introduction of computers to control the machine, to perform the immensely complex planning calculations, and CT scanners to provide the more precise diagnostic information required for planning three-dimensional radiotherapy has now completely altered the scenario Dynamic therapy is best used for tumours with a tortuous distribution and in such cases it has been demonstrated that the tumour volume irradiated is usually reduced by a factor of 2 and sometimes by as much as a factor of 3. To date, the advance of this technique has been hampered by non-existence of a commercial planning system capable of planning such treatments and also by the excessive time taken to perform manual checks on the dosimetry. The Royal Free Hospital has now developed a true three-dimensional planning system, which is complemented by a computerised technique for dosimetry checks. The project has now reached the stage when a commercial enterprise could convert this technological advance into a turn-key system, thus enabling any radiotherapy centre with a modern fully motorised linear accelerator to carry out dynamic treatments. The philosophy for the technique is indisputable and with the further knowledge of diagnostic techniques to provide absolute knowledge of the distribution of tumours, it will provide a very important advance in the treatment of cancer. A by-product of this development has been the introduction of fully automated, multi-field standard treatments under computer control. This technique should enable a linear accelerator to increase its workload by about 40%, an important feature in saving major capital costs.

PATIENT IMMOBILISATION

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The most important consideration is that patients be mentally and physically relaxed in preparation for treatment. We are communicating information regarding disease and treatment more thoroughly and several centres now offer relaxation classes to patients Some internal movement of organs (*e.g*, the bobbing of the larynx) is caused by anxiety but natural and unavoidable movement (*e.g.*, oesophagus, kidneys) should not be forgotten when using static imaging.

Treatment couches for external beam treatments on supervoltage units are at present flat and totally unyielding, to give parity between simulator, mould room, CT scanner and treatment couches. Small wonder then that patients may move slightly during treatment when not treated in a shell, as they may well be pivoting on their spinous processes A device must be found to cradle the patient comfortably whilst being itself unobtrusive to the beam. Is levitation the answer or is there a more down-to earth solution?

Couch modifications and gadgetry are needed to help us treat increasing numbers of patients swiftly, confidently and comfortably. Consideration of immobilisation reveals how important are meticulous mould room staff, wizard workshops and/or manufacturers with an eye to detail.

Mould room staff are not legally required to have any qualification; the only formal training available is for those who are medical physics technicians. These make up only a small percentage of those employed in mould rooms in the UK, others are recruited from radiographers, engineers or the man in the street. Is it not time that a good career structure and comprehensive training programme was agreed? Who should take responsibility for this?

Manufacturers have been very slow in the past to carry out consumer research into basic accessories required for their equipment. Is it not time that good robust accessories were offered for those departments finding difficulty in providing these, since workshop facilities vary so widely across the country?

HYPERTHERMIA

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The use of hyperthermia as a method of treatment for malignant disease is currently under intensive investigation in many centres The possibility of killing tumour cells by a modest rise in temperature of up to 42–50°C for periods of a few minutes to hours has been known for many years The effect is related both to the magnitude of the temperature and the duration of treatment. The interaction of hyperthermia with radiotherapy and some drugs has also been extensively documented recently. Laboratory work has established a very clear basis for the rationale of such therapy

Clinical implementation has been slow and limited by the technical difficulties of both heat delivery and measurement. Hyperthermia may be whole-body, regional or local and each technique presents its own problems. Whole-body heating is achieved by radiant heat cabinets or extracorporeal heating of blood but is limited to an upper temperature of around 42°C. Drugs may be given concomitantly but toxicity will also then be enhanced. Regional heating may be delivered surgically by limb perfusion through a pump oxygenator system; or deep in the abdomen and pelvis by microwave and radiofrequency assemblies Focusing with the latter is not currently possible

The most usual type of hyperthermia is given to relatively superficial nodules and node masses by microwave or radiofrequency appliances delivered through one or more applicator types of antennae. Ultrasound may also be used when tissue interfaces are not a problem.

The temperature and depths heated will depend on the frequency and power of the radiators, dielectric constants of the tissue traversed, and physiological cooling factors such as blood flow At present all thermometry is invasive, with thermistors or thermocouples. These may also interact with the electromagnetic radiators, and necessitate power switching during recording. Much remains to be solved in the technological developments before hyperthermia can be a routine treatment modality in the clinic

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HOW DO YOU DEFINE TREATMENT SUCCESS?

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In this 'State of the Art' review current methods of defining treatment success were discussed as well as some of the more historical ideas on cancer cure and some suggestions for future consideration.

There are several concepts of cancer cure (see Easson & Russell, 1968; Haybittle, 1983; Mould, 1983), including the specification of a cured proportion of patients, *C*, which can be estimated from a parametric statistical model such as the lognormal (see Boag, 1949, Mould & Boag, 1975) Typical values for *C* for cancer of the cervix are: Stage I. 0 57–0 71, Stage II 0.36–0.43, and Stage III. 0 14–0 27

Length of survival refers only to *quantity* of life whereas treatment success should also incorporate some measure of *quality* of life,' if possible on a quantitative scale. However, to date only qualitative scales are available such as the Karnofsky (Karnofsky & Burchenal, 1949) and the Host Performance Scale (American Joint Committee for Cancer Staging and End-Results Reporting, 1978). These are generally applicable scales, and for a more specific example, for cancer of the cervix, four rating systems for complications have recently (see Mould, 1985) been described by Rhomberg, Close, Nair & Jayaprakash, and Kaminska Rhomberg's is based on that by Kagan et al (1979) and is the most widely used system at present

For accurate statistics, or even any statistics at all, a well planned and efficient cancer registry is a prerequisite. Modifications to the Westminster Hospital Cancer Registry were described (Mould, 1982), including new software relevant to the Thames Cancer Registry requirements, updated hardware and plans to study the relationship between duration of symptoms and survival, and between disease-free time and survival, in order to try and obtain better indices of treatment success

WHAT THE RADIOGRAPHER WANTS

S. H. Crookes

Oncology and Radiotherapy Centre, General Hospital, Cheltenham

Radiography treatment teams require equipment which is adapted to their tasks and acceptable to the patient, and requires minimum attention from the physics department. Isocentres of modern machines are frequently too high for convenience, and need a better wedge system. A well thought-out maintenance and daily monitoring plan can prevent many interruptions to treatment. The introduction of computer systems has sometimes proved very frustrating in use. With increasing technological sophistication of equipment, cost-effectiveness becomes even more important. In the radiographers' view, this would be aided by—

Stable beam dosimetry with immediate switching between modalities; variable geometry diaphragms to facilitate beam shaping; automatic monitoring of patient centring; key parameters set at the control, particularly with isocentric treatments, to reduce excursions into the treatment room, self-calibration against a known standard, dynamic graphic display of key machine functions, updating of department statistics and provision of a disease register; a table-top which is translucent to radiation and light; computerised radiography for check films

WHAT NEXT?

I. C. P. Millar

MEL, Crawley, Sussex

Although much work has been done to study protons, mesons and neutrons the cost of producing a clinically useable beam has not been justified by the clinical results. Linear accelerators producing X-ray and electron beams up to 25 MeV are thus expected to be the main treatment machines in use in the foreseeable future.

The improvements in diagnosis and localisation that result from the use of magnetic resonance imaging and CT give better three-dimensional information on tumour shape, and the possibility exists to increase the dose to the tumour while reducing the dose to healthy tissue. Computers are, however, necessary not only to prepare the treatment plan but also to control the treatment machine. We are thus entering the era of computer-assisted radiotherapy which will require digitally controlled linear accelerators with integrated verification and recording systems. Computer assistance will provide the additional flexibility and control required to give more accurate treatments to more patients than is currently possible and thus, it is believed, to an improved success rate in the current years.

Biological effects of both non-ionising and ionising radiation

Abstracts of papers presented at the above meeting which was held on May 10, 1985 at Institute House, 36 Portland Place, London W1N 3DG

Chairman: Dr. S. B. Field

Quantitation of injury to skin following haematoporphyrin plus visible light, by J. V. Moore
Do microwaves induce chromosome aberrations? by D. C. Lloyd and R. D. Saunders
Effect of ultrasound on mast cell degranulation in normal skin, by M. Dyson and D. Luke
Non-thermal effects of ultrasound on V79 spheroids, by G. ter Haar, P. Loverock and J. Walling
Early effects of microwave hyperthermia on the rat kidney, by A. L. Busza, R. J. Dickinson and G. Rowlinson
Skin carcinogenesis in the mouse following uniform and non-uniform beta irradiation, by J. P. Williams, J. E. Coggle, M. W. Charles and J. Wells
Repair and repopulation in epithelial and vascular connective tissue in pig skin, by G. J. M. J. van den Aardweg, J. W. Hopewell and R. H. Simmonds
Divergent patterns of radiation response: adrenal gland vs kidney, by A. Michalowski, B. M. Cullen, J. Burgin and B. Reeves
Fluorocarbons and anaemia: effect on the irradiation response of tumours under hyperbaric oxygen, by A. Photiou
Measurement of cellular radiation response using ^{3}H-thymidine incorporation assay, by N. E. Fox and P. R. Twentyman
Cell kinetics assessed using bromodeoxyuridine and flow cytometry, by N. J. McNally and G. D. Wilson

QUANTITATION OF INJURY TO SKIN FOLLOWING HAEMATOPORPHYRIN PLUS VISIBLE LIGHT

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Oedema and necrosis of murine tail skin have been measured after the intravenous injection of an haematoporphyrin derivative (HPD) followed 24 h later by graded exposures of the tail to full-spectrum visible light from a quartz-halogen lamp (75 mW/cm^2 of white light incident on the skin surface). End-points used were the degree of oedema, measured by whole-tail volume, and the proportion of mice in a dose-group that developed full-thickness skin necrosis.

Oedema developed within 24 h and the severity was a function of the HPD dose and the length of light exposure. Necrosis occurred after a minimum of five days. The time of onset was an inverse function of the exposure time. 'Probit' plots of the proportion of necroses vs light exposure yielded values for ND_{50} (exposure corresponding to a 50% incidence) and 1/slope (time to increase incidence from 16 to 50% or 50 to 84%). At the high, but non-toxic, dose of 2 mg HPD/mouse the ND_{50} was 18 min and 1/slope 4 min for pigmented BDF mice. Halving the HPD dose increased the ND_{50} by a factor of 1.9 but the slope remained 'steep' (1/slope = 6 min). Albino BALCc mice were markedly more sensitive to 2 mg HPD plus light than BDF1 mice, the ND_{50} was 7 min. Of potential relevance to the efficacy of HPD and light as an anticancer treatment was the observation of a strong 'oxygen effect', clamping the tail 10 min before and during exposures up to 110 min prevented any toxic effect (expressed as oedema and necrosis). In summary, skin necrosis after HPD plus visible light varied with HPD dose, and for a given HPD dose was a steep function of exposure time to visible light.

EFFECT OF ULTRASOUND ON MAST CELL DEGRANULATION IN NORMAL SKIN

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Dermal mast cells are exposed to ultrasound whenever it is used clinically. Their degranulation induces inflammation. The degranulation of mast cells in the intact skin of adult male Wistar rats treated *in vivo* with therapeutic levels of ultrasound was examined quantitatively by light microscopy in formaldehyde-fixed sections stained with toluidine blue. At a frequency of 3 MHz, spatial-average, temporal-average intensities of at least 1.5 W/cm^2 were necessary to stimulate degranulation to a level significantly greater than that of mock-irradiated skin. Previous investigations have shown that lower intensities stimulate degranulation in the mast cells of injured tissue, suggesting that those of intact skin are less sensitive to ultrasound. The effects of variation in spatial-average temporal-average intensity, in spatial-average pulse-average intensity and in frequency suggest that the mechanism involved in the stimulation of mast cell degranulation in normal skin is primarily thermal.

NON-THERMAL EFFECTS OF ULTRASOUND ON V79 SPHEROIDS

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Non-thermal mechanisms for cell killing have been identified when cell suspensions, maintained at hyperthermic temperatures (41.5°C–45°C), are irradiated with ultrasound. This report considers the effect of ultrasound irradiation on suspensions of spheroids.

Spheroids consisting of V79 Chinese hamster lung fibroblasts were cultured, and used at 200 μm, 400 μm or 600 μm diameter. 2.6 MHz continuous-wave ultrasound was used throughout the study. Following treatment, spheroids were either (i) plated individually into agar-coated Linbro wells and their diameter measured daily, (ii) disaggregated into single cell suspensions and plated for clonogenic assay, or (iii) fixed in glutaraldehyde for transmission electron microscopy.

At 37°C no difference in growth was seen between spheroids irradiated with ultrasound, at intensities up to 1.6 W cm^{-2}, for one hour and those that were not. Similarly, no difference was seen between the 37°C control spheroid growth curves and those maintained at 41.5°C for an hour either with or without ultrasound. Spheroids maintained at 43°C for an hour exhibit a growth delay of about 2 days (measured at 6 times their original volume), ultrasound irradiation of the spheroids at 43°C increases the growth delay significantly depending on the intensity.

Single cell experiments show that there was a similar relationship between surviving fraction and growth delay for heat alone and for heat plus ultrasound.

Electron microscopy of spheroids held at 43°C showed, amongst other features, aggregation of organelles around the nucleus, clumping of chromatin and some fragmentation of the nucleolus. Ultrasound irradiation during heating led to additional vacuolation, condensation or complete disappearance of the nucleolus, gross nuclear damage and separation of the cells within the spheroid. Quantimet analysis of cells showed that heat led to an increase in the cell's area but that there was no change in nuclear size. There was no difference in cell or nuclear size between the irradiated and unirradiated cells at 43°C.

EARLY EFFECTS OF MICROWAVE HYPERTHERMIA ON THE RAT KIDNEY

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A microcomputer-based system has been assembled which automatically controls the delivery of microwave hyperthermia to the exposed left kidney of anaesthetised female BD9 rats. Thermometry was carried out by using copper-constantan thermocouples mounted in 31G hypodermic needles inserted into the cortex and medulla. Skin and rectal temperatures were also monitored. All hyperthermia treatments were converted to "Minutes Equivalent at 43°C" (min Eq 43), which was calculated continuously throughout the experiment. Treatment stopped when a preset heat dose (min Eq 43) had been delivered.

Histological sections of heated kidneys showed a sharp demarcation between affected and apparently normal tissue. Immediately following a treatment of 20 min Eq 43, the heated area demonstrates less intense staining, swollen tubular epithelial cells and increased intertubular distance. By seven days following treatment, the heated region was necrotic and was surrounded by calcified tissue which was infiltrated by fibroblasts and some collagen. There appeared to be a limited proliferation of the epithelial cells of the Bowman's capsule immediately adjacent to this region.

In order to quantitate the heat injury, measurements of vascular volume were made using ^{51}Cr-labelled erythrocytes at times up to 30 days after treatment, with the results expressed as the ratio of the vascular volume between the left (treated) and right (untreated) kidneys of the same animal. No difference from control was observed following heating for 10 min Eq 43. Following heating for 20 min Eq 43, there was a transient increase in vascular volume ratio immediately after treatment. This returned to control levels by day 1, then decreased to a minimum at day 3. By day 7 after treatment the ratio was the same as the control.

Preliminary data obtained following heating for 30 min Eq 43 showed no difference from control values at days 1 and 3, though by day 7 after heating it appeared that the vascular volume ratio was beginning to decrease. Experiments are in progress to measure vascular volume at very early and late times after 30 min Eq 43 to compare with the effects seen after milder treatments.

SKIN CARCINOGENESIS IN THE MOUSE FOLLOWING UNIFORM AND NON-UNIFORM BETA IRRADIATION

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A study of 1200 male SAS/4 mice was carried out using uniform and non-uniform thulium-170 beta sources. The uniform source was 8.6 cm^2 and the two non-uniform sources were arrays of either 32 sources of 2 mm diam. or 8 sources of 2 mm diam. distributed over 8 cm^2. Beta doses between 20 and 1000 Gy for the uniform source and 20 and 500 Gy for the non-uniform sources were used. The mice were observed throughout their life-span; all animals were autopsied and any tumours were kept for histopathological examination. The tumour dose-response curve for uniform irradiation shows an almost linear increase in incidence to a peak of 95% between the doses of 150–200 Gy followed by a slight fall to a plateau value of about 70% at higher doses. The non-uniform results showed a 30% reduction in the tumour incidence from the 32-point array at the lower doses but rising to the uniform incidence level at 500 Gy. The 8-point array showed a significantly lower tumour incidence. The data indicated that the greater the non-uniformity the lower the tumour incidence. However, none of the dose-response curves showed any evidence of a threshold. Histopathology to date indicates a ratio between dermal, epidermal and miscellaneous induced tumours of 20 : 1 : 1.

REPAIR AND REPOPULATION IN EPITHELIAL AND VASCULAR CONNECTIVE TISSUE IN PIG SKIN

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Split-dose studies were performed to assess the repair and repopulation characteristics of epithelial and dermal vascular elements in pig skin. In the first 16 weeks after irradiation the severity of the epidermal reaction (moist desquamation) and of the dermal response (dusky/mauve erythema and necrosis) was scored.

After single doses from strontium-90 plaques, the dose required to produce moist desquamation after 4–6 weeks, in 50% of the fields irradiated (ED_{50}) was 28 Gy. After irradiations using two equal doses, with an interval of one day between fractions, the ED_{50} value for moist desquamation was 35 Gy, indicating a D_2–D_1 value of 7 Gy. This represents the repair of sublethal damage. No significant additional repair occurred between 1 and 14 days. With longer intervals between fractions, the ED_{50} value increased with time, reaching 56.5 Gy with an interval of 42 days between fractions. This indicated a D_2–D_1 value of 29.5 Gy, which suggested complete repair of the damage caused by the first dose. A somewhat higher D_2–D_1 value of 36.5 Gy was obtained with an inter-fraction interval of 63 days. From these data we could not determine whether the epithelial repopulation was an exponential process initiated from the day of the first dose or a linear process starting after 14 days.

After single doses of X rays the ED_{50} value for dermal necrosis, which appears 10–16 weeks after irradiation, was 20.5 Gy. Split-dose studies with a 1 day interval between doses resulted in a spared dose (sublethal damage repair) of 4.5 Gy. With intervals > 28 days between fractions the ED_{50} values for dermal necrosis increased up to a value of 36 Gy with an interval of 112 days. Similar results were obtained using an assay based on the less severe dusky/mauve erythema reaction.

Repair and repopulation in the acute phase were also assessed using the less severe, but subjective, early erythema reaction between 3 and 9 weeks after exposure. The values for the recovered dose obtained using the assay were only in agreement with those based on the incidence of moist desquamation for inter-fraction intervals of up to 28 days. With longer inter-fraction intervals the results were not in agreement. This suggests the need for caution in the use of arbitrary skin scoring scales, into which a number of visual observations are incorporated.

DIVERGENT PATTERNS OF RADIATION RESPONSE: ADRENAL GLAND VS KIDNEY

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In a study of unilateral irradiation of the mouse left kidney and left adrenal with 15 Gy of X rays, the rate and extent of the weight loss was different for the two organs. Further differences between the weight changes of the left kidney and left adrenal were observed when the contralateral unirradiated organs were surgically removed.

The onset of compensatory hypertrophy (CH) in response to excision of the contralateral organ in unirradiated mice was immediate in the left kidney and the weight increased by 50%, whereas in the adrenal the onset of CH was delayed and amounted to 20% only.

The weight loss of the irradiated kidney was initially slow, possibly accelerating and amounted to 25%, 20 weeks after irradiation. The weight loss of the irradiated adrenal was initially fast, later decelerating and reached 50%, 20 weeks after irradiation.

CH of the unirradiated right kidney was apparent when the weight loss of the irradiated left kidney was only 10% and the degree of CH 20 weeks after irradiation was 30% (marginal overcompensation). By contrast, CH of the unirradiated right adrenal was not apparent until the irradiated left adrenal had lost 40% of its initial weight and amounted to 20% 20 weeks after irradiation, leaving a considerable deficit in the total adrenal mass.

Surgical removal of the unirradiated kidney elicited a biphasic response of the irradiated kidney; 4 weeks after right nephrectomy CH had reached 25% but later the organ lost weight again. Right adrenalectomy initiated little or no hypertrophy in the irradiated left adrenal but it may have delayed its weight loss by several weeks.

These results show that while physiological control of adrenal cell mass is strikingly slack, that of the kidneys is rather tight. The two organs also differ in the way in which the rate of their post-irradiation weight loss changes with time after exposure.

FLUOROCARBONS AND ANAEMIA: EFFECT ON THE IRRADIATION RESPONSE OF TUMOURS UNDER HYPERBARIC OXYGEN

Andrew Photiou

Richard Dimbleby Department of Cancer Research, St. Thomas's Hospital Medical School, London SE1 7EH

Attempts were made to increase the effectiveness of hyperbaric oxygen (HPO) in reducing the hypoxic fraction of the C3H mammary tumour at the time of X irradiation. A number of methods were employed either alone or in combination, in order to achieve this.

Anaesthesia (ketamine and diazepam) was found to enhance regrowth delay under HPO in agreement with previous published data. Oxygen toxicity was observed in a few anaesthetised mice when at a pressure of three atmospheres absolute.

The blood substitute FC-43, given intravenously (0.35 ml/25 g) 1–2 h prior to irradiation to anaesthetised mice, enhanced the tumour response when mice were treated under HPO, but not under air-breathing conditions. A 25 Gy exposure caused a significant ($p < 0.01$) regrowth delay of 44 days in the fluorocarbon-treated mice compared with delays of 29 days and 18.5 days for mice anaesthetised and unanaesthetised respectively.

In subsequent experiments, anaemia was induced in an attempt to combine tumour blood flow improvement with increased oxygen content afforded by HPO/FC-43/anaesthesia. To this end, the viscosity of whole blood in mice was reduced by inducing a moderate level of anaemia with a single IP injection of phenylhydrazine HCl (40 mg kg^{-1}). Haematocrit was reduced from 42% to 32%. Regrowth delay was reduced from 44 days for the FC-43 treated group, to 37.3 days ($p < 0.02$) in the anaemic group, for an exposure of 25 Gy.

Mouse data with fluorocarbons are encouraging. Fluorochemical emulsions may have uses as potential adjuncts to radiotherapy.

MEASUREMENT OF CELLULAR RADIATION RESPONSE USING ^{3}H-THYMIDINE INCORPORATION ASSAY

N. E. Fox and P. R. Twentyman

MRC Clinical Oncology and Radiotherapeutics Unit, Cambridge, CB2 2QH

We have previously shown that the sensitivity to X radiation and cytotoxic drugs of cells from an established mouse tumour and a human tumour xenograft can be effectively determined using a 4-day radionuclide uptake assay. We have now extended these studies to examine the radiation response of cells from a range of xenograft tumours of both high and low clonogenic capacities.

The radiation response curves of two small-cell lung cancer lines, COR-L24 (low plating efficiency) and NCI-H69 (high plating efficiency), were similar when determined by the clonogenic assay. The responses of the two lines as determined by the ^{3}H-thymidine uptake assay, however, were very different, with COR-L24 appearing to be much less sensitive to radiation. This and other experiments showed that high plating efficiency lines give a reasonable agreement between results obtained using the different assays, whilst low plating efficiency lines do not In the ^{3}H-thymidine uptake assay, the isotope was routinely added on day 4. Using times other than day 4 did not markedly change the conclusions for either COR-L24 or NCI-H69.

For COR-L24, growth curve experiments showed that cell numbers at 4 days after 0, 1 5 and 3 Gy were similar. However for NCI-H69 the cell numbers at day 4 following these radiation doses were very different. We have found that it takes many days for the effect of radiation to become manifest in the case of COR-L24 and that a 4-day isotope uptake assay cannot be used to measure the radiation sensitivity of this cell line

CELL KINETICS ASSESSED USING BROMODEOXYURIDINE AND FLOW CYTOMETRY

N. J. McNally and G. D. Wilson

Gray Laboratory of the Cancer Research Campaign, Mount Vernon Hospital, Northwood, Middx. HA6 2RN

Flow cytometry was used to measure simultaneously cellular DNA content using propidium iodide and BrdU uptake into cellular DNA using a monoclonal antibody against BrdU combined with a fluorescein-labelled goat anti-mouse antibody. In this way the cell kinetics of normal and perturbed populations could be measured rapidly and quantitatively. We have used the technique to measure the cell kinetics of V79 cells growing at different temperatures and of mouse tumours following irradiation with X rays or neutrons It was possible to measure a G2 block in tumours following a dose of 5 Gy X rays. Doses of X rays and neutrons which give the same tumour growth delay give different delays in G2 immediately after irradiation. We present preliminary results measuring the labelling index of human tumours labelled with BrdU *in vitro* and in the patient. The technique is a rapid one which has many applications in tumour radiobiology.

Book reviews

Atlas of Obstetric, Gynecologic and Perinatal Ultrasonography. Ed. by Kenneth J. W. Taylor, pp. x+433, 1985 (Churchill Livingstone, New York), £155.00.
ISBN 0–443–08443–2

This volume is designed to provide an atlas for obstetricans and gynaecologists and is part of a more comprehensive atlas of ultrasonography published for radiologists The title is somewhat misleading in that the perinatal component of the perinatal section refers only to the examination of the neonatal head.

The overall qulity of the illustrations is good. Many of the ultrasound images have corresponding line drawings by way of explanation, which is particularly helpful to the beginner. However, throughout the book many images have no headings and the reader is expected to refer back over several pages for explanations. The illustrations are generously spaced which has no doubt increased the cost. Throughout the book, reference lists are short but carefully chosen.

The opening chapters on ultrasound physics and artefacts are not specifically aimed at the subject content of this volume but are more suited to a general textbook of ultrasound. However, the general principles of ultrasound physics are well described and most common artefacts are discussed.

The content of the gynaecology section is very uneven, merely four short pages being devoted to uterine fibroids but six pages to Turner's syndrome and 12 pages to endometriosis However, the section on ectopic pregnancy is particularly well covered and the obstetric section is fairly comprehensive and well written. The helpful diagrams of fetal attitude juxtaposed proves a useful aid to interpretation of the images.

British readers will find the inclusion of breast scanning in such a volume unusual. This short section is well illustrated and scans relate well to the corresponding radiographs.

The final 54 pages are devoted to neonatal head scanning There is a predictable emphasis on the diagnosis of intracranial haemorrhage but it is disappointing that so little space is devoted to the appearance of ischaemic lesions and there is no mention of the ultrasound diagnosis of cerebral oedema.

Overall, the content is unbalanced and, considering the length of the book, not very comprehensive. This book may be suitable for its intended audience of obstetricans and gynaecologists but will not appeal to many radiologists.

HEATHER ANDREWS

Fundamentals of Nuclear Medicine, Handbook of Nuclear Medicine, Vol. 1/1. Ed. by H Kriegel, pp. 515, 1985 (Gustav Fischer Verlag, Stuttgart), DM.19 80.
ISBN 3–437–10828–x

This is the first volume of a series of 11 aimed at reviewing the whole subject of nuclear medicine. Whilst volumes 1/2 and 1/3 will be dedicated to *in vitro* methodology and radiopharmacy, respectively, volumes 2–11 will review the subjects of cardiology, endocrinology, bones and tumours, kidneys, lungs, gastroenterology, ENT, eye, neurology, haematology, paediatrics and oncology.

Thus, this is a major effort, by well known German editors, to provide an in-depth review of the entire subject of the application of the radionuclide tracer methods to Medicine.

In this first volume, fundamental information concerning technology, biophysics, nuclear biology, radiopharmacy, radiation protection and data processing is given, with individual chapters describing the radiation detectors and methods, autoradiography, neutron activation analysis and even nuclear magnetic resonance imaging.

As in all efforts of this magnitude, rapid publication is necessary to ensure that the information is up to date. This will be an additional challenge to the editors who are, however, particularly well equipped to meet this challenge. Volume 1 will be of interest only to those who can master the German language, although four out of the 10 chapters are written in English. There is a wealth of information in Volume 1 and it augurs well for the forthcoming volumes. The price (DM.19.80) is highly competitive and gives extremely good value for money. We recommend this book for the attention of libraries and departments of Nuclear Medicine; there will clearly be a wider individual readership in Central Europe.

P. ELL

Instructions to authors

Please keep manuscripts brief and include only those illustrations essential to an understanding of the text.

Much time and correspondence will be saved if authors pay careful attention to these detailed instructions especially as regards references (see below).

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Communications from North America, Continental Europe, Australasia or South Africa should preferably be submitted to the most appropriate of the following Associate Editors.

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MANUSCRIPT. The manuscript should be typewritten in English on one side of the paper only with double spacing and margins of at least 25 mm on both sides and at the top. Pages should be numbered. Two clear copies must be submitted. The address given in the title should be that of the department(s) or hospital(s) at which the work was carried out. If any author has subsequently moved to a new address, this should be given as a footnote. Degrees and diplomas of authors should be given but not more than three for each author. Tables (numbered I, II, etc.) should be given on separate sheets, and each should have a short descriptive title. Legends for illustrations, including diagrams and graphs, should be set out on a separate sheet, and denoted Fig. 1, 2, etc. The initial letter of trade or proprietary names should be a capital. Mathematical expressions should be set out very clearly. Paragraphs should be indented.

UNITS, SYMBOLS AND ABBREVIATIONS. Authors should use the International System of Units (SI) (NPL, 1982). Units of radiation should be given in SI with the old units in brackets if necessary; thus 1 Sv (100 rem), 200 cGy (rad), 1 MBq (27 μCi). THE BRITISH JOURNAL OF RADIOLOGY, May 1981, contained two useful articles on this subject, by the BIR Working Party on SI units and by W. A. Jennings. A handy Conversion Card may be obtained from the Institute at the address above, price 35p. On the question of quantities and units for radiation dosimetry, three recommendations from the British Committee on Radiation Units and Measurements (BCRU, 1980, 1982a, b) are worth consulting. The publication *Units, Symbols and Abbreviations: a Guide for Biological and Medical Editors and Authors* (Royal Society of Medicine, 1977) will also be found helpful

DIAGRAMS AND GRAPHS. Diagrams and graphs, including numerals and lettering, should be clearly drawn in black ink for photographic reproduction to a width of 76 mm (exceptionally 156 mm). Good quality photographic prints or the original art work should be supplied. Care should be taken that details such as numbering and experimental points remain legible after photographic reduction. Computer print-outs are seldom satisfactory. The figure number, author's name and title of article should be on the back of each illustration, either pencilled lightly or on a tacky label.

Authors of physics papers will find advice on drawing diagrams, particularly electrical circuits, in *Notes for Authors* issued by the Institute of Physics and the Physical Society in 1976 (revised 1983).

RADIOGRAPHS. Unmounted prints not larger than whole plate, 216 × 152 mm, and not smaller than half plate should be supplied with MSS, if the prints are not of sufficiently high standard for reproduction purposes the author will be required to submit the original radiographs and to defray the cost of making prints. Tracings of sections of prints are acceptable when necessary for additional clarification. Hospital illustrators and photographers are usually familiar with the style of drawing or print which will give the best reproduction.

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Examples

Cohen, M. D., Smith, J. A. & Greenman, G. G., 1983. Ultrasound diagnosis of liquid-filled lesions in children. *British Journal of Radiology, 56*, 527–530.

Michael, B. D. & Harrop, H. A., 1980. Time scale and mechanism of radiosensitization and radioprotection at the cellular level. In *Radiation Sensitizers*. Ed. by L. W. Brady (Masson, New York), pp. 164–170.

All references must appear both in the text and in the bibliography.

ABSTRACTS. Papers (other than case reports and technical notes) should be accompanied by an abstract. This abstract is not part of the paper, but is intended to convey the content of the paper, to draw attention to all new information and to the main conclusions, and should be intelligible in itself without reference to the paper. An abstract should not normally exceed 200 words.

CORRESPONDENCE. Letters for publication in the correspondence section of the journal may be accepted on any matters of interest to readers of this journal.

SHORT COMMUNICATIONS. These are reports of initial studies in new areas, and comments which are too speculative or provocative for a normal paper. They should be kept as short as possible and must on no account exceed two pages of the journal. No abstract is required. They will be published with the minimum delay.

CASE OF THE MONTH. These are short papers reporting a recognised but rare abnormality, or are teaching cases with points of general interest that might be seen at an examination. They will occupy no more than two pages and should, therefore, be no more than 1700 words long, less approx. 200 words for each illustration included. The relevant history and initial radiographs will appear on a right-hand page, presenting a specific problem to the reader. Overleaf will appear comments, with the results of further investigations and a conclusion, followed by a brief and up-to-date review of the subject with a maximum of five references. The names of no more than three authors will be printed. Radiotherapy and oncology, as well as diagnostic, papers will be welcomed for this feature.

OFFPRINTS AND REPRINTS. Twenty-five free "as printed" offprints of each paper will be supplied. A form for ordering additional offprints, bound offprints etc. will be sent to the authors with proofs for correction. This form should be returned, giving the address for offprints, even when additional offprints are *not* required.

SUPPLEMENTS. Special monographs which are too long for publication within the journal, or detailed reports of certain meetings, may be considered for publication as a Supplement.

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Jennings, W. A., 1981. How much do you know about quantities and units? *British Journal of Radiology, 54*, 381–383.

National Physical Laboratory, 1982. *The International System of Units.* (*SI*) Ed. by D. T. Goldman and R. J. Bell. Her Majesty's Stationery Office, London (£3.95).

The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, 1977. *Units, Symbols and Abbreviations. a Guide for Biological and Medical Editors and Authors* (£2).

Radiation warning signs

Apart from any other considerations arising from legislation such as the *Ionising Radiations Regulations*, the *Approved Code of Practice* etc., warning signs of various sorts which are displayed in hospitals and other public places must conform with *The Safety Signs Regulations 1980 SI No. 1471* and *British Standards BS 3510: 1968* and *BS 5378. 1980 British Standard No. 5378 Part I* (1980) contains details of the approved style and colouration of these signs. It will be an offence after January 1, 1986, to continue to display signs which do not conform with this Standard, and in fact, many hospital departments have already adopted signs which satisfy the necessary requirements.

However, it is perhaps time that radiation protection advisers, radiation protection supervisors, and other persons involved should look at the signs displayed in the departments for which they are responsible from other points of view. Under the new *Ionising Radiations Regulations*, controlled areas will have to be precisely specified, and, in order to avoid the necessity of drawing up Schemes of Work to cover such situations as arise when cleaners enter X-ray rooms after normal working hours, these areas will require to be designated temporally as well as topographically, and some means is thus required to ensure that the warning signs required under *Regulation 8–(5) (a)* and paragraph 47 of the *Approved Code of Practice* are only displayed under the appropriate circumstances

A further potential problem has been identified in hospitals in Avon, where fire crews have standing orders relating to the procedures to be followed in the event of encountering these signs at the site of a fire These procedures involve sending a radio message for breathing equipment and radiation monitoring equipment, all of which is unnecessary except in a very few special situations involving cobalt teletherapy units, radionuclide stores, and radiopharmacies.

It is, therefore, suggested that in these locations where there are quantities of radionuclides assessed by the relevant local fire authority to represent a hazard in the event of fire, a special fire symbol should be used, perhaps consisting of the existing signs so as to conform with the above legislative requirements, but mounted on a red background with or without the word "FIRE" displayed in black on the red background. Earlier types of radiation warning signs incorporating the word "FIRE", and said to have been approved by the Radioactive Committee of the Fire Brigades Advisory Council, were available from Messrs Jencons (Scientific) Ltd, of Leighton Buzzard.

The relevant fire authorities and local fire officers should be notified of the intention to display these signs, which should not be put up without consultation, and they should be provided with a list of all the locations where they are displayed and a list with the type and activities of the various radionuclides involved. Furthermore, a map of these locations should be prepared, copies of which should be provided for the relevant fire authorities, and large printed copies of these plans should be displayed inside the main entrances to the hospitals concerned.

One of the features of current health and safety legislation is that all signs which are exhibited should be correct and specific to the hazard to which they draw attention. It is thus incumbent upon all parties concerned in the area of radiation protection to ensure that these requirements are being observed in their own departments, hospitals and laboratories.

D. Gifford

Forthcoming legislative package on radiation protection

The long-running saga which has been a feature of our lives for so long now is finally reaching a climax, and the book of the play can now be purchased from the various branches of HMSO. Two of the three volumes are now available: The Ionising Radiations Regulations 1985. Statutory Instrument 1985 No. 1333. £5.80, ISBN 0 11 057333 1.

The timetable of implementation is as follows:

Made: August 23, 1985.
Laid before Parliament: September 4, 1985.
Coming into operation for the purposes of Regulation 10 October 1, 1985.
For all other purposes: January 1, 1986.

Approved Code of Practice: The protection of persons against ionising radiation arising from any work activity. £5.65, ISBN 0 11 883838 5.

The Notes for Guidance are not yet available.

DHSS Radiodiagnostic Department, Health Building Note

A new Health Building Note, HBN 6, Radiodiagnostic Department, has been published. It is the latest addition to the new series of Building Notes which provide guidance on briefing, planning and design for those concerned with the provision of health buildings. Building notes describe the standards of accommodation and engineering services which the Department, in consultation with representatives from the National Health Service and appropriate professional bodies, recommends for use in the NHS. The standards are applicable to the upgrading of existing health buildings as well as the design of new buildings.

HBN 6 contains the most recent recommendations for the planning and design of the facilities required for a radiodiagnostic department. It replaces the existing guidance entitled "Diagnostic X-Ray Department" which was issued in 1961 (revised 1968) The guidance reflects the current policies in this specialist field and is much more comprehensive than the existing Note.

The new Building Note gives guidance on the provision of radiodiagnostic and imaging services. The Note includes a variety of new functional requirements, such as new processing facilities and special rooms with higher environmental standards to make it possible to increase efficiency

There is also a Design Briefing System document (DBS 6) for use with each copy of the building note. This is intended to help specify the user requirements which form part of the design brief. DBS adopts a check list approach. Like the building notes, DBS can be applied to upgradings of existing buildings or planning for new ones.

A set containing the two documents can be ordered from the usual HMSO agents and through booksellers at a total cost of £9.60 Additional copies of the DBS 6 for use in a project can be obtained at £3.20 each

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Press Releases

Human body explored by interactive laser video

Micro Scope plc, Odeon Productions and Pioneer (Japan) Inc. together have produced an interactive Anatomy Project, using laser video disc, which was presented at the Barbican Centre, London, on August 13–15, 1985. New techniques, including fibre - optics, lasers, CT, nuclear magnetic resonance, computer-enhanced imaging and Quantel's Video Paintbox, have been used in conjunction with more traditional techniques to present a detailed anatomy of the human body.

A distinguished editorial board of anatomists include the editors of *Gray's Anatomy*, Wolfe's Anatomical Colour Atlases, and professors from the Royal College of Surgeons

The result is a work aimed at all levels of study in the medical profession Anatomy, the fundamental study of the form and function of the human body, has been run down to an extent where such a system will be "of immediate and immense value", according to many eminent authorities on both sides of the Atlantic The Anatomy Project offers the opportunity of individual exploration at any individual pace, enabling users to explore, probe and dissect any part of the human body that takes their interest.

Micro Scope plc is best known for its work with private viewdata systems; they have years of experience in implementing intelligent man–machine interactive systems. Odeon is the production company of Terence Dixon, the award winning television science documentary producer. Some of his best known series are "Botanic Man" (with David Bellamy), "The Human Race" (with Desmond Morris) and "The Enchanted Loom" (about the human brain) Pioneer are participating in this project with their laser disc technology.

For more overall technical information on the whole project, call John McNulty, R & D Director, on (0923) 28466.

New magnetic resonance centre in Detroit

A centre for magnetic resonance imaging is soon to be built at Harper Hospital, Detroit, USA. The co-operative project brings together Wayne State University School of Medicine, the Wayne State University Department of Chemistry, the Michigan Cancer Foundation, the Comprehensive Cancer Centre of Metropolitan Detroit and the entire Detroit Medical Centre. The imaging centre will be part of the radiology department of Harper Hospital.

The complex will house three magnetic resonance devices. Two devices will be dedicated entirely to research, while the other will be used to diagnose patients' diseases and monitor their progress.

One of the centre's major functions will be to study the cost-effectiveness of magnetic resonance imaging, and to determine precisely what clinical conditions call for its use. The overall cost of the project is expected to be $8.8 million.

For further information contact Harper-Grace Hospitals, 3990 John R., Detroit, Michigan 48201.

New revolving vial shield holder

Van Mullekom Nuclear Fields have introduced a revolving vial shield holder with six or 10 lead containers. The new Vial Carrousel is especially developed for use in a nuclear-medical environment such as hospitals. It is a hand-operated revolving construction with a mechanical built-in stop for every one of the six or 10 vial positions.

Vial shields have lead walls 6 mm thick, in which lead-glass panels may be fitted. A revolving shield is fitted to the bottom of each container. The shielding is sufficient to reduce the radiation level from 925 MBq of $^{99}\text{Tc}^{m}$ to background level

The Vial Carrousel will be marketed by Van Mullekom Nuclear Fields B.V. at Vortum-Mullem, The Netherlands, and Nuclear Fields (Aust) Pty. Ltd. at St. Marys, New South Wales, Australia. For further details contact either of these addresses

Picker X-ray unit rings changes in the twelfth century

A novel use of the newly installed Picker CT unit at Mount Vernon Hospital, Norwood, London was demonstrated recently when a number of twelfth-century timber beams, brought from the Museum of London, were radiographed to help pinpoint their age.

The wooden beams were excavated from a riverfront archaeological site in Billingsgate where they were found intact, having been protected by river silt for 500 years. They once formed part of a pier of a thriving twelfth-century waterfront. After a temporary exhibition at the Museum of London in Autumn 1986, they will be on permanent display at the Docklands Museum, opening in 1987, where the reconstructed pier will be the UK's largest preserved wooden artefact.

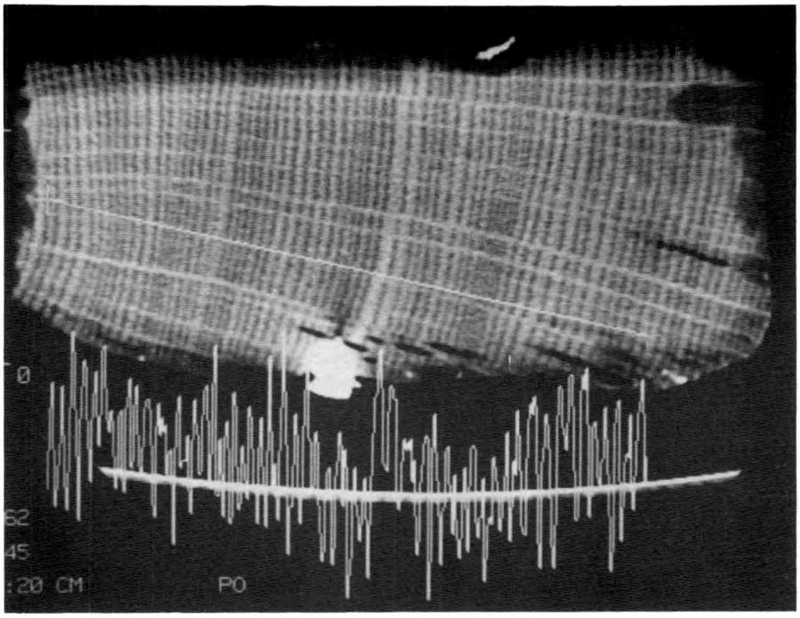
This is not the first time Picker equipment has been used by archaeologists; an MRI unit was used in the famous "Pete Marsh" 2500-year-old murder case. Staff at the Museum of London were most grateful to the Mt Vernon and Picker staff and said that the results obtained were even better than had been hoped for. Using CT scanning, it is possible to obtain the data without harming the specimen, whereas dating wood using other methods often means removing a section.

For further information contact Iain MacRae, Marketing Services Manager, Picker International Ltd, P.O. Box No. 2, East Lane, Wembley, Middx HA9 7PR (Tel. 01-904 1288).

Two CT units for Sheffield's Royal Hallamshire Hospital

Two Picker CT units were recently installed at the Royal Hallamshire Hospital, Sheffield, in what is the first European site to house two CT units, delivered together, and supplied by a single manufacturer. A cable link will be established later this year between the CT scanners and the Radiotherapy Planning Unit at the Weston Park Hospital, half a mile away. The CT images enable the stereotactic gamma unit, also at Weston Park Hospital, to be used to its full potential. One of only three such units in the world, the stereotactic gamma unit is used for the radiotherapeutic treatment of deep-lying tumours.

For further information contact Philip Eckstein, Picker International Ltd, PO Box 2, East Lane, Wembley, Middlesex HA9 7PR (Tel. 01-904 1288).



CT image of the wooden beam. The density profile between the two cross marks allows the tree rings to be easily recorded.

New family of universal radiotherapy simulators

Varian Associates, Inc. has announced a completely new family of universal radiotherapy simulators, the Ximatron C-Series: three upgradeable Ximatron models that each provide Varian's unique "Exact Simulation". The three Ximatron models differ primarily in their imaging systems, so that the model best suited to the buyers requirements can be selected without compromise of mechanical simulation performance. The three models are the Ximatron CX three-phase fluoroscopic system; the CF with single-phase fluoroscopic system; and the CR with single-phase radiographic system. The Ximatron CR is easily upgradeable on-site to either the CF or CX models.

"Exact Simulation" is achieved by adding to universal simulation the precise duplication of the treatment-field geometries and couch-top structure of the treatment unit. The treatment units' actual field-defining accessories can be attached directly to a C-Series simulator; and the Ximatrons' special removable panel couch-top structure allows simulation of solid, centre-spine or side-rail couch-top structures typical of treatment units. These units have highly stable stand-mounted gantries. The collimator control system allows fully independent movement of the collimator and the individual field wires for simulating new treatment techniques.

Quick and convenient patient setup is assured through a new control console and a new "intelligent" pendant based on extensive use of microprocessors. The control console's colour graphic displays make possible greatly enhanced communications between operator and machine.

For further information contact Robert M. Potenza, Varian Associates Inc., 611 Hansen Way, Palo Alto, California 94025 (Tel. 415-424 5033).

BIR Calendar Events

Unless otherwise indicated, enquiries about the following events should be addressed to the Assistant Secretary Programme, British Institute of Radiology, 36 Portland Place, London W1N 3DG (Tel. 01-580 4085).
The meetings are at 36 Portland Place unless otherwise stated.
Attendance is open to non-members

British Institute of Radiology and Royal College of Radiologists Magnetic Resonance Update UMIST Manchester
January 10–11, 1986
University of Manchester Institute of Science and Technology
An important two-day meeting organised by the Royal College of Radiologists, jointly with the British Institute of Radiology. Consisting of both clinical and workshop sessions, the meeting is designed for both radiologists and colleagues in other disciplines.

The clinical sessions will address the role of magnetic resonance in clinical problem solving and in particular how magnetic resonance can be integrated with other techniques

The workshop sessions, led by teams consisting of a consultant radiologist, physicist and radiographer will address problems concerned with installation and operation of magnetic resonance scanners on a day-to-day basis

Speakers to include: Prof J. J. K. Best (Edinburgh), Dr J.H. Buckley (Nottingham), Dr G M. Bydder (London), Dr D H. Carr (London), Dr. G Cherryman (Sutton), Prof. G du Boulay (London), Dr D.G. Gadian (London), Prof. I. Isherwood (Manchester), Dr J.P R Jenkins (Manchester), Dr. R.J Johnson (Manchester), Dr D M. Kean (Edinburgh), Prof. J S Orr (London), Ms. J. Pennock (London), Dr. F.W Smith (Aberdeen), Prof. R. E Steiner (London), Prof. B.S Worthington (Nottingham).

Programmes and registration forms can be obtained from The Meetings Secretary, The Royal College of Radiologists, 38 Portland Place, London W1N 3DG (Tel. 01-636 4432/3).

Members and Fellows of the Royal College of Radiologists will receive these automatically.

Endoscopy and its Relationship to Radiology
January 16, 1986 at 5.45
Joint BIR/RCR/RSM meeting organised by BIR
Institute House
Chairman Dr J. N. Glanville
Speakers. Dr A. Chapman, Dr R. Frost, Dr D. Beckley, Dr D Shepard, Dr M. I. Lavelle and Dr D. Cumberland.

Quantitation and New Techniques in Nuclear Medicine
February 12, 1986 at 10.30 am
Joint IPSM/BIR meeting
The meeting will deal with data acquisition and processing in nuclear medicine. The day's proceedings will be divided into three sessions, dealing with nuclear cardiology, SPECT, and antibody imaging.

Lymphomas
February 20, 1986
The Finzi Lecture by Dr E. Glatstein. "Non-Hodgkin's Lymphoma"
Joint RSM/RCR/BIR all-day meeting organised by RSM

Radiobiology Meeting
February 21, 1986 at 11.00 am
All-day general non-topic meeting organised by the Radiobiology Committee (proffered papers).

Clinical Use of Electrons
February 26, 1986 at 10 00 am
Chairmen: Dr W. F. White and Mr E. G. A. Aird.
Speakers Dr G. Pitchford, Dr S. Klevenhagen, Dr M. F. Spittle, Dr G. Ribeiro, Dr P Williams, Mr K. Larkin, Mr U Graf and Dr T. Landberg.
Joint BIR/IPSM meeting organised by BIR

Abdominal Sepsis
March 26, 1986
Including special lecture by Dr P C. Freeny.
Joint RSM/RCR/BIR all-day meeting organised by RSM and held at the RSM

Annual Dinner
April 10, 1986
Holiday Inn, Bristol

Annual General Meeting of the BIR
May 14, 1986
Members only.

Radiology '86
April 9–11, 1986
Bristol
44th Annual Congress and Exhibition
Incorporating the joint spring meeting of the Institute with the Royal College of Radiologists and the Section of Radiology of the Royal Society of Medicine. It will be held in the picturesque setting of the Bristol waterfront.
The scientific programme will encourage discussion of contemporary aspects of the radiological sciences and will include:
BIR Mackenzie Davidson Memorial Lecture (Dr A Margulis: "The Impact of New Imaging Technology on Health Care, Research and Teaching")
BIR Mayneord Lecture, sponsored by 3M UK Plc (Mr G. Higson. "Seeing Things More Clearly")
RCR George Simon Lecture (Professor N. M. Bleehen. "Raleigh's Revenge")
All-day Seminar—Buying for Radiology organised with the Association of National Health Service Supplies Officers
All-day Seminar—Biological Basis of Radiological Protection and its Application to Risk Assessment
Proffered Papers
Large Technical and Scientific Exhibition
Annual Dinner, April 10

Safety of Ultrasound and Presidential address
May 15, 1986
Middlesex Hospital Medical School, London W1
Includes the Presidential Address to be given by Dr P N T Wells "The prudent use of ultrasound"

Progress in Tumour Radiobiology
May 16, 1986 at 11.00 am
Organised by the Radiobiology Committee (proffered papers).

The Assurance of Quality in Medical Imaging
May 21, 1986
Middlesex Hospital Medical School
All-day meeting organised by the Industry Committee

Conversazione
June 19, 1986 at 7.00 pm
Royal Society of Medicine, London W1
Incorporating the Silvanus Thompson Memorial Lecture: "Seeing through illusion", by Professor R L Gregory

Meetings, Courses, Notices

As a service to our readers, the title, date and place of meetings and contact address will be inserted free of charge· any additional information will be charged at £1.50 per printed line, per insertion Please contact the Managing Editor.

Courses in Abdominal and Obstetric Ultrasound
January 6–December 8, 1986
The Johns Hopkins Medical Institutions, Baltimore, Maryland
Basic practicum; Advanced obstetrics and gynecology, Visiting Physicians, Advanced practicum in ultrasound.
Further details: Joan Mosmiller, Department of Radiology, Johns Hopkins Hospital, Baltimore, Maryland 21205 USA (Tel 301-955 8450).

International Continuing Medical Education Series
Controversies in Medicine and Surgery
January 17–25, 1986
January 24–February 1, 1986
St. Moritz, Switzerland

Controversies in Medicine
February 28–March 6, 1986
March 7–14, 1986
March 14–21, 1986
March 21–28, 1986
Barbados

Controversies in Medicine
April 30–May 8, 1986
May 7–15, 1986
Paris/Versailles, France

Update on Laser Therapy
June 25–July 3, 1986
July 2–10, 1986
Heidelberg, Germany

Controversies in Medicine
August 14–22, 1986
August 21–29, 1986
London, England
Further details Dr Barry M Manuel, Department of CME, Boston University School of Medicine, 80 E. Concord Street, Boston, MA 02118, USA (Tel 617-638 4605)

15th Annual Meeting and Postgraduate Course Presented by The Society of Gastrointestinal Radiologists
January 19–24, 1986
Acapulco, Mexico
Further details. Lynne K. Tiras Program Coordinator, The Office of Continuing Education, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030, USA (Tel 713-799 6020).

Radiation Incidents—Modelling, Regulations and Experience
January 28, 1986
City Conference Centre, London EC1
Further details Programme Committee Secretary, Professor J. H. Martin, Department of Medical Biophysics, Building 15, Park Wynd, University of Dundee, Dundee DD1 4HN.

8th Carvet: International Meeting on Magnetic Resonance Imaging
February 2–7, 1986
Rome, Italy
Further details Plinio Rossi, M.D., 2a Cattedra di Radiologia, Policlinico Umberto 1, 00161 Rome, Italy (Tel 06-4955602)

Conference on Radionuclide Labelled Cellular Blood Elements
February 3–6, 1986
Bloemfontein, South Africa
Further details· The Secretariat S. 56, MRC Conference Division, PO Box 70, 7505 Tygerberg, South Africa.

Computers for the Practising Physician: Update 1986
February 5–7, 1986
Contemporary Resort at Walt Disney World, Lake Buena Vista, Florida
Further details Barry M. Manuel, Department of Continuing Medical Education, Boston University School of Medicine, 80 E Concord Street, Boston, MA 02118, USA (Tel. 617-638 4605)

Symposium on Nuclear Particle Accelerators in Medicine
February 10–14, 1986
Cape Town, South Africa
Further details: the Secretariat S.55, MRC Conference Division, PO Box 70, 7505 Tygerberg, South Africa.

Magnetic Resonance Imaging Update
February 16–19, 1986
Hyatt Palm Beaches, West Palm Beach, Florida
Further details Department of CME, Boston University School of Medicine, 80 E. Concord Street, Boston, MA 02118 USA (Tel. 617-638 4605).

Clinical Oncology Symposium: Investigation Techniques in Radiation Oncology
February 21–22, 1986
Jarvis Hall, 66 Portland Place, London
Further details· The Meetings Secretary, The Royal College of Radiologists, 38 Portland Place, London W1N 3DG (Tel 01-636 4432/3).

Symposium on Dysphagia
February 27–March 1, 1986
The Johns Hopkins Medical Institutions, Baltimore, Maryland
Further details: Jeanne Ryan, Program Coordinator, Office of Continuing Education, The Johns Hopkins University School of Medicine, 720 Rutland Avenue, Turner 22, Baltimore, MD 21205, USA (Tel. 301-955 6046)

Interventional Radiology Course
March 3–7, 1986
Hotel St George, Sheffield
Further details: Dr D. C. Cumberland, Northern General Hospital, Sheffield S5 7AU (Tel 0742-387253 ext.4828).

Computers in Medicine—A Workshop for Beginners
March 10–11, 1986
Monte Carlo
Further details· Computers in Medicine, Dr Hans O Beckmann, Bitterstr. 13, D 1000 Berlin 33, West Germany

International Symposium on the Optimization of Radiation Protection
March 10–14, 1986
Organised by the International Atomic Energy Agency, Vienna, Austria
Closing date for applications to attend (via Department of Energy) December 13, 1985.
Further details Mr M Pankhurst, Atomic Energy Division, Department of Energy, Thames House South, Millbank, London SW1P 4QJ.

European Workshop on Nuclear Magnetic Resonance in Medicine—4th Annual Meeting Joint Meeting with World Health Organization
March 12–15, 1986
Monte Carlo
Further details. European Workshop on NMR in Medicine, Dr R. N Muller/Dr P. A. Rinck, State University of Mons, Medical Faculty, B 7000 Mons, Belgium (Tel 32-65-315171 ext. 228).

3rd Congress of the South African Medical Ultrasound Society
March 14–17, 1986
Johannesburg Sun
Further details: Congress Director, PO Box 6705, Johannesburg 2000, South Africa.

Combined Course in Clinical Oncology and Radiotherapeutics
March 17–21, 1986
The Postgraduate Medical Centre, Lancaster House, Glasgow
A one week course suitable for postgraduate students with an interest in the management of malignant disease and candidates preparing for the F R C R. Part II Examinations.

The programme will include tutorial sessions, case presentations and topics related to recent advances Multi-modality treatment of specific tumours will be discussed in detail

Meetings will commence at 9 00 am on Monday March 17, 1986, in the Postgraduate Medical Centre, Lancaster House, Lancaster Crescent, Glasgow
The course fee will be £175.

Residential accommodation will be available in a nearby modern University Hall of Residence and, if required, this should be indicated on the application form as the number of rooms is limited

Further details and application forms Dean of Postgraduate Medicine, University of Glasgow, Glasgow, G12 8QQ (Tel 041-339 8855, ext 7274).

Obstetric and Neonatal Blood Flow
April 8–9, 1986
King's College Hospital, London
Further details. Biological Engineering Society, Royal College of surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN (Tel. 01-242 7750).

The Actinides
April 9, 1986
City Conference Centre, 76 Mark Lane, London EC3
This meeting is organised by the Society for Radiological Protection and will be followed by the Society's Annual General Meeting
Further details. Programme Committee Secretary, Professor J H. Martin, Department of Medical Biophysics, Building 15, Park Wynd, University of Dundee, Dundee DD1 4HN

Symposium on Malignant Disease and the Skin
April 11–12, 1986
University of Liverpool
Further details Prof. C. F. H Vickers, Department of Dermatology, Royal Liverpool Hospital

British Nuclear Medicine Society Annual Congress
April 13–16, 1986
at Imperial College, London SW7
Further details. Mrs A Taylor, BNMS, Conference Secretary, 22 Leinster Avenue, East Sheen, London S14 7JP.

Biological and Therapeutic Aspects of Cancer Metastasis
April 14–17, 1986
Vitoria, Spain
Further details: Meeting Secretariat, Apartado 1299, 48080 Bilbao, Spain.

Images of Living Brain Chemistry: Neuroreceptors
April 18–19, 1986
Baltimore, Maryland
Further details: Diane Heydinger, Program Coordinator, Turner 22, 720 Rutland Avenue, Baltimore, MD 21205, USA (Tel. 301-955 6046).

The National Institutes of Health Consensus Development Conference on Neurological Applications of Positron Emission Tomography
April 21–23, 1986
Clinical Center of the National Institutes of Health, Bethesda, Maryland
Further details Shelley Clark (Tel. 301-468 6555).

1st International Conference on the Clinical Application of Photosensitization for Diagnosis and Treatment
April 30–May 2, 1986
Tokyo
Further details. Dr Yoshihiro Hayata, Tokyo Medical College Hospital, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan.

4th International Radiology Congress: Radiology in Salzburg
September 7–13, 1986
Salzburg, Austria
Further details Dr D. Beatty Crawford, Department of Radiology, University of Connecticut Health Center, Farmington, CT 06032 USA (Tel. 203-674 3322).

Errata
In the September *Bulletin*, page B54, an advertisement for "Postrad" appeared. We wish to make clear that the School is known as the North West Lancashire School of Radiography and that the Open Tech Unit is independent from the School of Radiography.

Library news

The BIR Library is open weekdays 9am–6pm

The Librarian, Mrs Gunnel Ingham, is in attendance Tuesdays and Thursdays 11am–4pm; Mrs Diana Jasper, daily 10am–6pm

The journal stock includes more than 100 titles Though journals may not be taken out of the library, there is a photocopy service, also available by post.

Most books (excepting the historical collection) are available on loan.

Further information telephone 01-580 4085.

Recent additions to the Library

Carroll, Q B: Fuchs's principles of radiographic exposure, processing and quality control. 3rd edit. 1985
Cohen, M. & Mitchell, J. S. (Compilers): Cobalt-60 teletherapy—a compendium of international practice. IAEA, 1984
CEC. protocol for X-ray dosimetry. Radiation protection report. 1985
Freeman, L M (Ed.). Clinical radionuclide imaging. Vols 1–2 3rd edit. 1984
Jaffe, C. C (Ed.). Vascular and Doppler ultrasound (Clinics in diagnostic ultrasound. 13) 1984
Jarrit, P. H. & Ell, P. J.: Gamma camera emission tomography. 1984
Lemke, H U et al (Eds). Computer assisted radiology. Proceedings CAR 1985
Mould, R F.: Radiation protection in hospitals. 1985
Radioactive Substances Act. HMSO 1984
Reynolds, M. V.. How to succeed as a radiographer. Gevaert Ltd., 1950's
Royal Commission on Environmental Pollution. 10th report HMSO, 1984
Simeone, J. (Ed): Co-ordinated diagnostic imaging (Clinics in diagnostic ultrasound. 14). 1984
WHO: Extremely low frequency (ELF) fields. (Environmental health criteria. 35). 1984

BIR Publications

Basic Clinical Ultrasound
Hylton B. Meire and Pat Farrant. 170pp. 99 ill. 1982 **£12.00**

Central Axis Depth Dose Data for Use in Radiotherapy
British Journal of Radiology Supplement 17. 1983 **£8.00**

Treatment Simulators
(Applications of Modern Technology in Radiotherapy)
British Journal of Radiology Supplement 16. Revised 1981 **£3.50**

Quality Assurance
Proceedings of a CEC/CRAD Scientific Symposium on
Criteria and Methods for Quality Assurance in Medical
X-Ray Diagnosis. Udine (Italy), April 1984.
British Journal of Radiology Supplement 18. 1985 **£16.00**

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British Journal of Radiology. Special Report 17 (*published 1980*)

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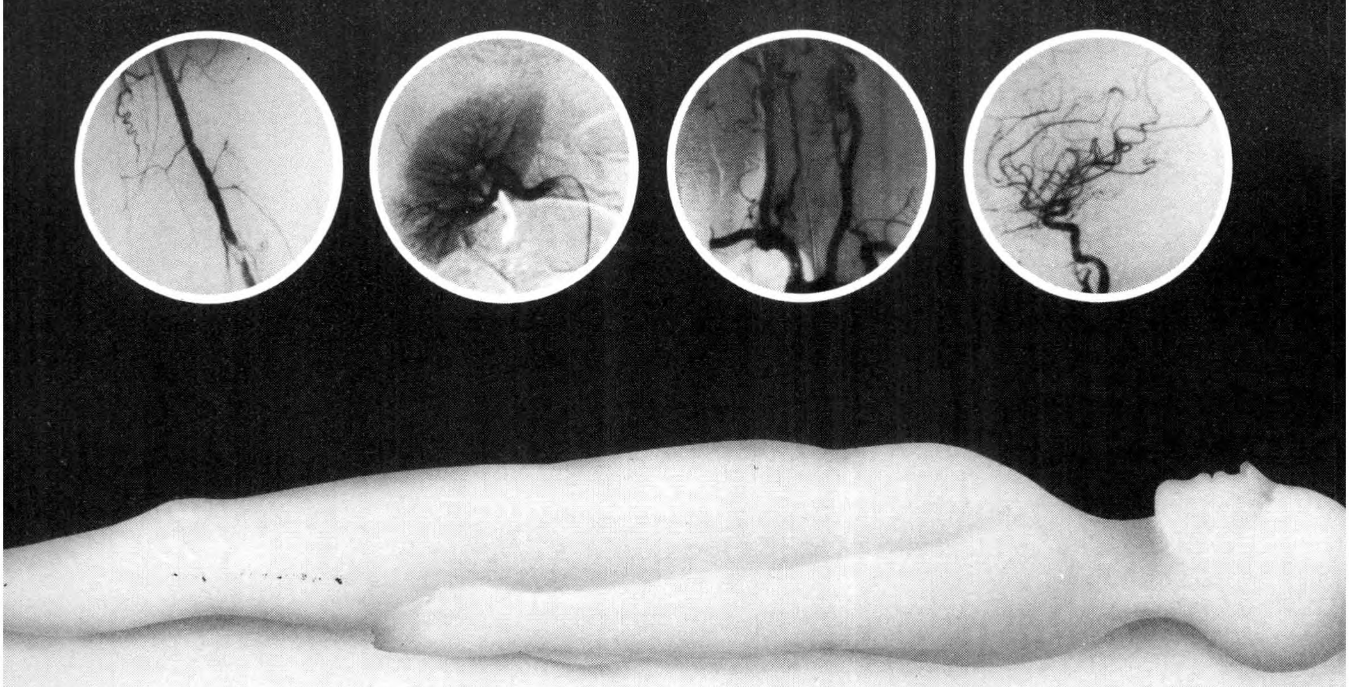

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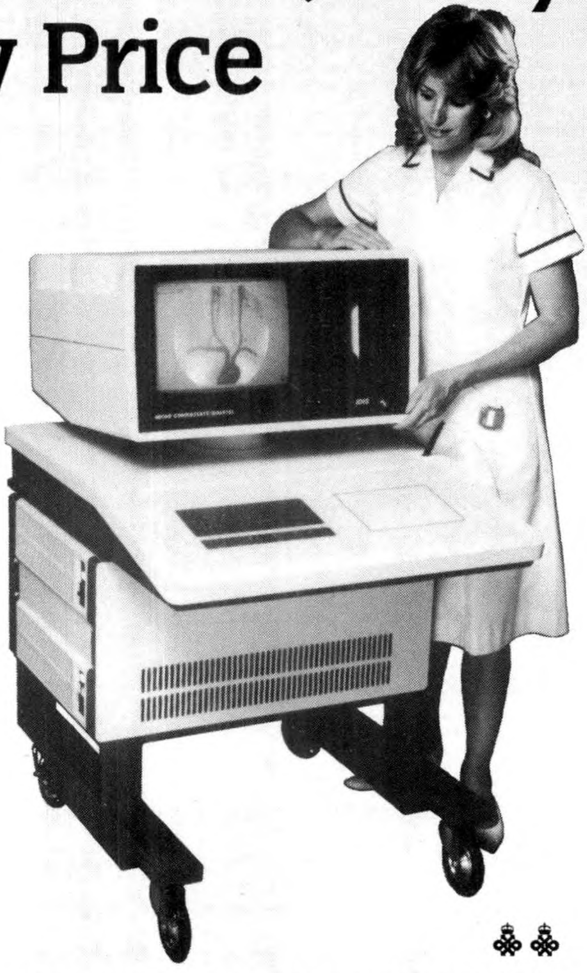

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(continued from outside back cover)

Page

Proceedings of The British Institute of Radiology
  Radiation oncology–the state of the art. May 17, 1985 85
  Biological effects of both non-ionising and ionising radiation. May 10, 1985 88
Instructions to authors 93

Book reviews

Page

Radiocontrast agents. Handbook of experimental pharmacology, Vol. 73. *M. Sovak* (Ed.) 12
Abdominal ultrasonography, 2nd edit. *B. B. Goldberg* (Ed.) 12
Assessment of skeletal maturity and prediction of adult height (TW^2 method). *Tanner, Whitehouse, Cameron, Marshal, Healy and Goldstein* 18
Doppler echocardiography. *N. C. Nanda* (Ed.) 18
Head and spine imaging. *C. F. Gazalez, C. B. Grossman and J. C. Masden* 40
A handbook of radioactivity measurements and procedures. *NRCP Report 58*, 2nd edit. 40
Cell clones—manual of mammalian cell techniques. *C. S. Potten and J. H. Hendry* (Eds.) 52
Gynaecologic cancer. *A. A. Forastière* 52
Imaging anatomy of the head and spine. *H. M. Snitzlein and F. R. R-Murtagh* 60
Ultrasonics for medical applications (2) (Acta Electronica, Vol. 26, Nos 1/2). 60
Atlas of obstetric, gynecologic and perinatal ultrasonography. *K. J. W. Taylor* (Ed.) 92
Fundamentals of nuclear medicine. Handbook of nuclear medicine, Vol. 1/1. *H. Kriegel* (Ed.) 92

BIR Bulletin and Calendar Events *facing page* 94

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★ RCR George Simon Lecture (Professor N M Bleehen—Raleigh's Revenge)
★ All day Seminar—Buying for Radiology organised with the Association of National Health Service Supplies Officers
★ All day Seminar—Biological Basis of Radiological Protection and its Application to Risk Assessment
★ Proffered Papers (late submissions will be considered)
★ Large Technical and Scientific Exhibition

For further information and registration details please apply to:

The Assistant Secretary (Programme)
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VOL 59 NO 697 JANUARY 1986

The British Journal of Radiology

Contents

Page

Editorial: Diagnostic radiological examinations of women of reproductive capacity 1
M. J. Day

The rise and fall of the ten-day rule 3
J. G. B. Russell

Parametric imaging using digital subtraction angiography 7
G. J. S. Hunter, J. V. Hunter and N. J. G. Brown

Ultrasound of the hip: a review of the applications of a new technique 13
L. Berman, A. Catterall and H. B. Meire

Clinical comparison of a new technetium 99m DTPA aerosol delivery system with krypton 81m 19
J. P. Finn, M. J. Myers, K. M. Nair and J. P. Lavender

Focal sparing in fatty infiltration of the liver 25
C. M. Kissin, E. A. Bellamy, D. O. Cosgrove, N. Slack and J. E. Husband

Diverticular disease (adenomyomatosis) of the gallbladder: a radiological–pathological survey 29
I. Williams, G. Slavin, A. Cox, P. Simpson and G. de Lacey

A comparison of simplified and standard methods for the measurement of glomerular filtration rate and renal tubular function 35
A. Notghi, M. V. Merrick, C. Ferrington and J. L. Anderton

Delayed reactions to urographic contrast media 41
P. N. Panto and P. Davies

The long-term hazards of the treatment of thyroid cancer with radioiodine 45
C. J. Edmonds and T. Smith

Thermal enhancement of radiation damage in previously irradiated mouse intestine 53
S. P. Hume and J. C. L. Marigold

The RBE for mouse bladders after irradiation with 1 to 8 fractions of d(4)+Be neutrons 61
F. Stewart, V. Randhawa and R. Maughan

Case reports

Generalised enchondromatosis associated with haemangiomas, soft-tissue calcifications and hemihypertrophy 69
E. M. D. Phelan, H. M. L. Carty and S. Kalos

Hypertrophic osteoarthropathy in a young child with congenital cyanotic heart disease 75
S. Katariya, P. J. Prasad, R. K. Marwaha and J. Chandra

Case of the month

Pain in the hand in the presence of mediastinal mass 77
I. P. Hicks and D. H. Carr

Correspondence

Hexabrix and gallbladder visualisation 79
D. Rickards and P. Dawson

Biliary tract opacification following intravenous Hexabrix: a normal phenomenon detectable by computed tomography 79
P. Bellamy and D. Patrick

Indium-111 radioactivity in breast milk 80
D. Butt and K. F. Szaz

Clinically derived dose–effect relationship for hyperthermia given in combination with low-dose radiotherapy 80
J. A. G. Holt

Reply
J. van der Zee, G. C. van Rhoon, J. L. Wike-Hooley and H. S. Reinhold

The absence of tissue specificity in MRI using *in vivo* T_1 or T_2 determination: true biological variation or technical artefact? 82
M. A. Smith and D. G. Taylor

Radioprotection by ascorbate *in vitro*: temperature-dependent uptake 83
M. R. L. Stratford and R. J. Hodgkiss

(*continued on inside back cover*)

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Volume 59 Number 69
February 198

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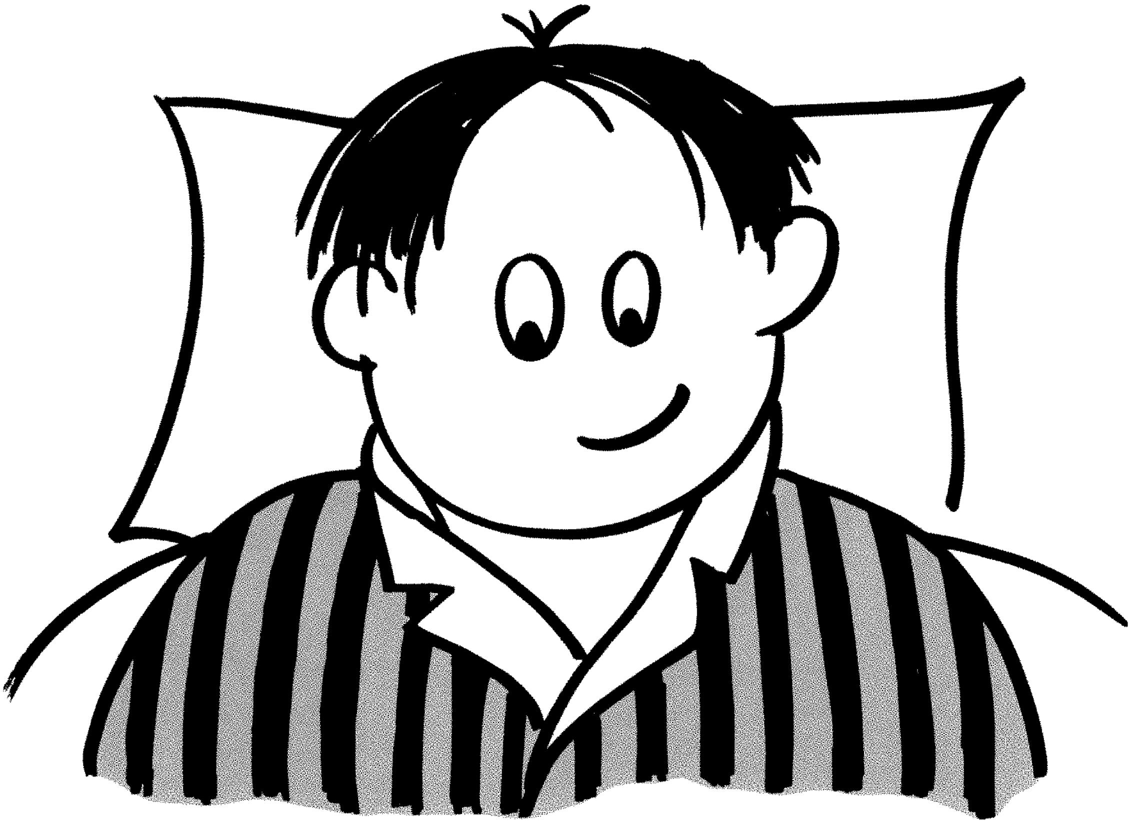

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Prescribing Information
Presentation: Nubain* Injection, 20mg of nalbuphine hydrochloride in 2ml ampoules.
Uses: For the relief of moderate to severe pain.
Dosage and Administration: 10-20mg for a 70kg individual, adjusted according to the severity of pain, physical status of the patient and concomitant medications. Nubain is not recommended for children.
Contra-Indications: Hypersensitivity to Nubain.
Precautions and Warnings: Use with care in known and potential opioid abusers. Also care in active patients who may drive or operate machinery. Caution in patients with impaired respiration. Safety for use in myocardial infarction is not yet established. Caution and dose reduction in patients with impaired renal or hepatic function. Safe use not established in pregnancy and in conditions of raised intracranial pressure. Abrupt discontinuation of chronic therapy may produce withdrawal symptoms.
Side Effects: The most frequent reaction is sedation. Also sweating, nausea, vomiting, dizziness, dry mouth, vertigo and headache and other opioid effects may occur.
Product Licence No.: 4524/0003. **NHS Price:** £11.60 per box of 10 x 2ml ampoules.

References: 1. Julien RM. Effects of nalbuphine on normal and oxymorphone – depressed ventilatory responses to carbon dioxide challenge. Anaesthesiology 1982; 57: No 3A. 2. Fahmy NR, Sunder N, Soter NA. A comparison of histamine releasing properties and hemodynamic effects of morphine and nalbuphine in humans. Anesth Analg 1984;63:175. 3. Vatashsky E, Haskel Y. The effect of nalbuphine (Nubain®) compared to morphine and fentanyl on common bile duct pressure. Curr Ther Res 1985;37,1:95-102. 4. Shah M, Rosen M, Vickers MD. Effect of premedication and diazepam, morphine or nalbuphine on gastrointestinal motility after surgery. Br J. Anaesth. 1984;56: 1235-8.
Further information is available on request from Du Pont (UK) Limited, Pharmaceuticals, Wedgwood Way, Stevenage, Hertfordshire SG1 4QN. Telephone: (0438) 734549.
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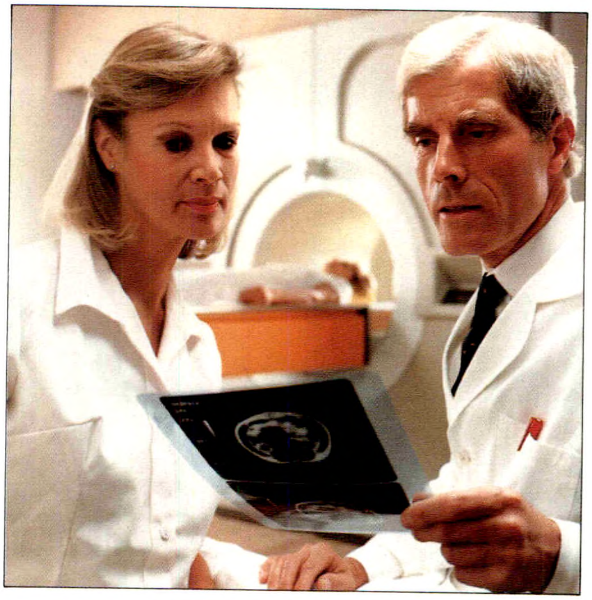

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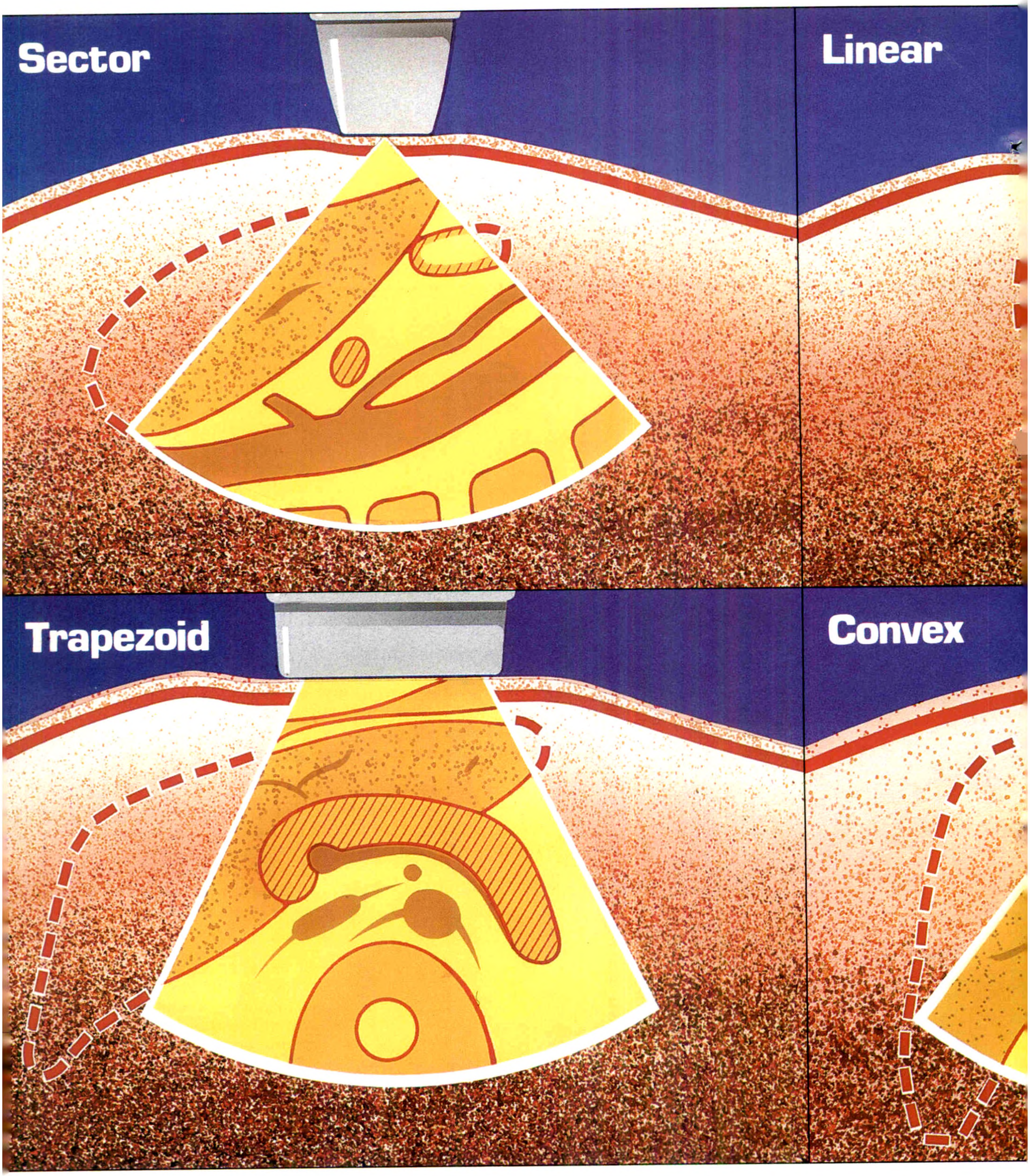

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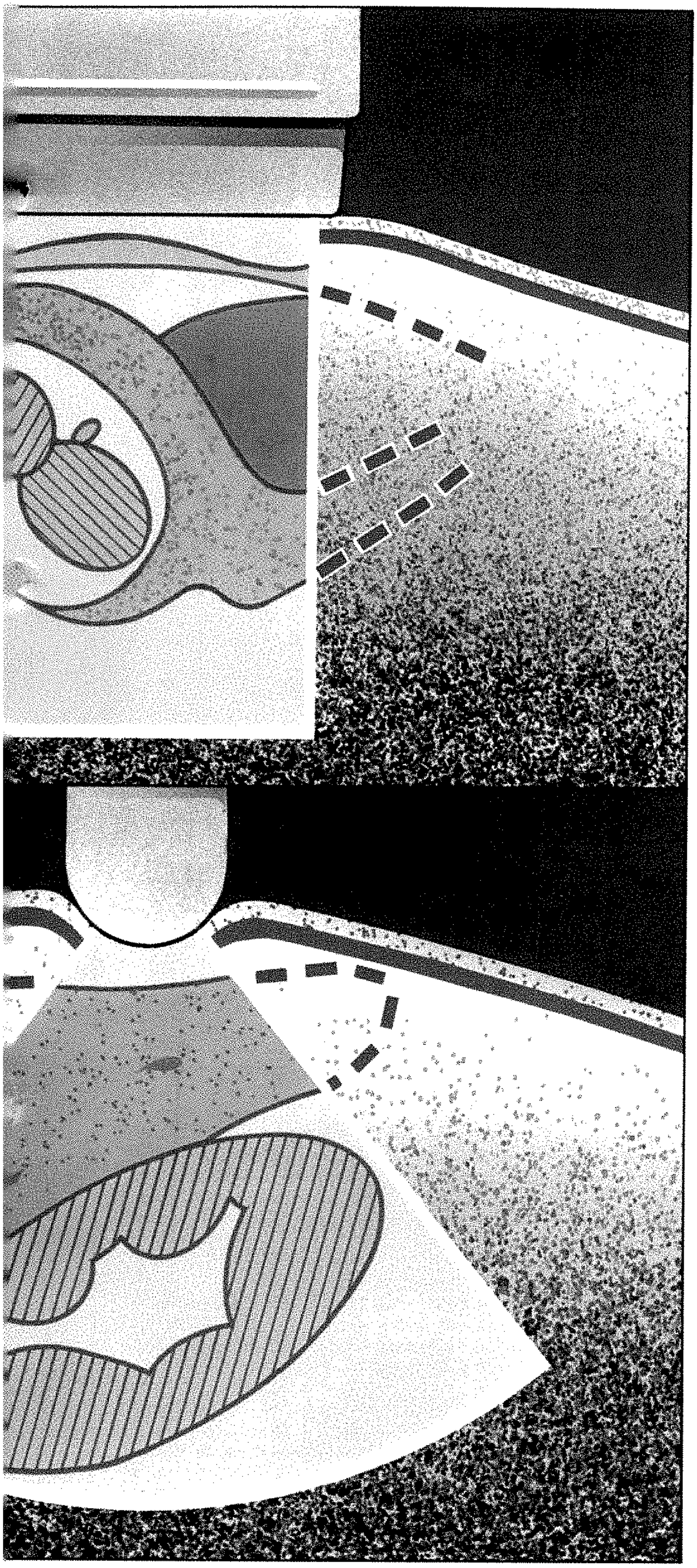

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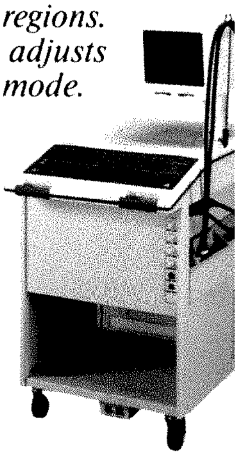

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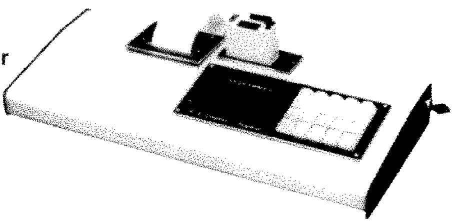

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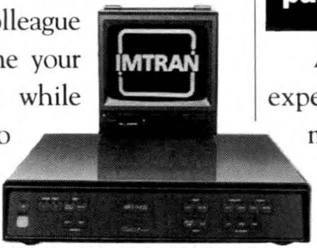

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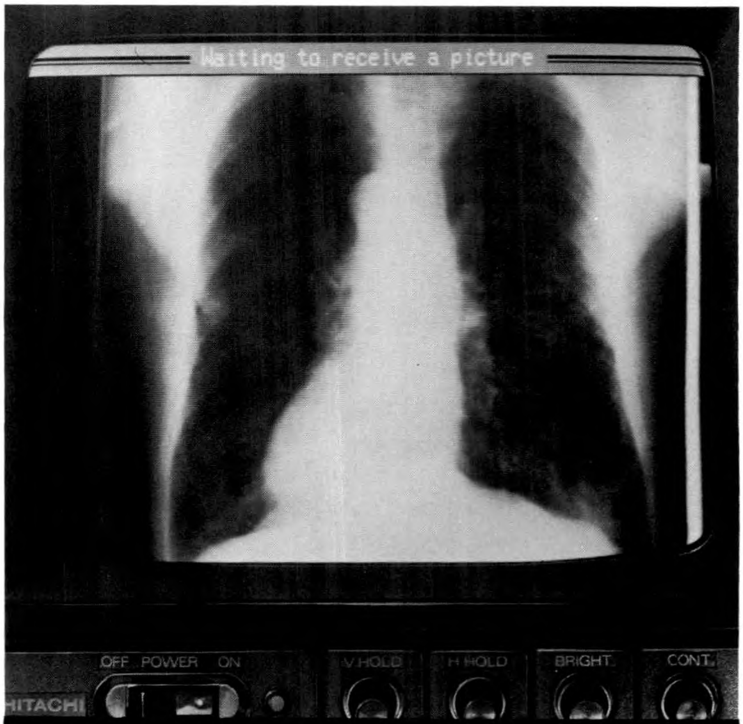

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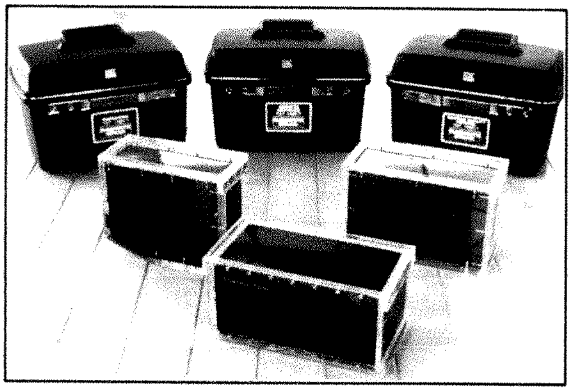

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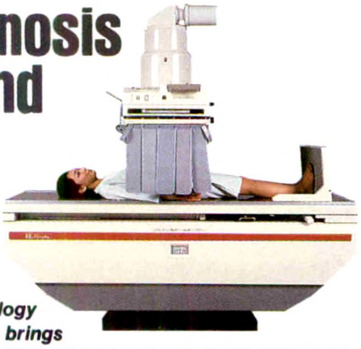

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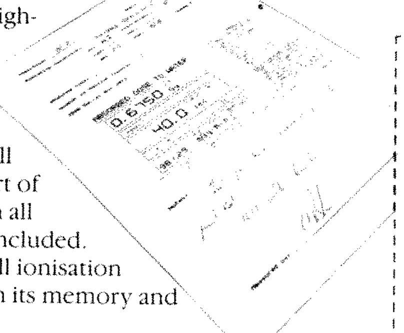

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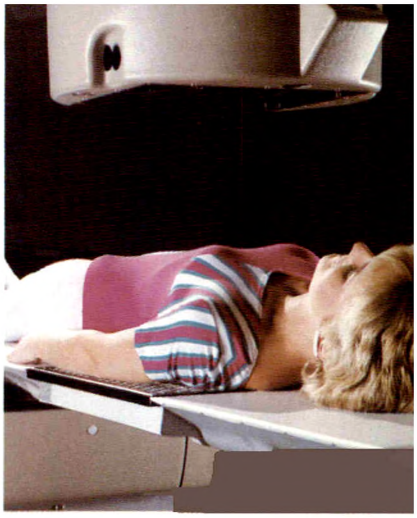

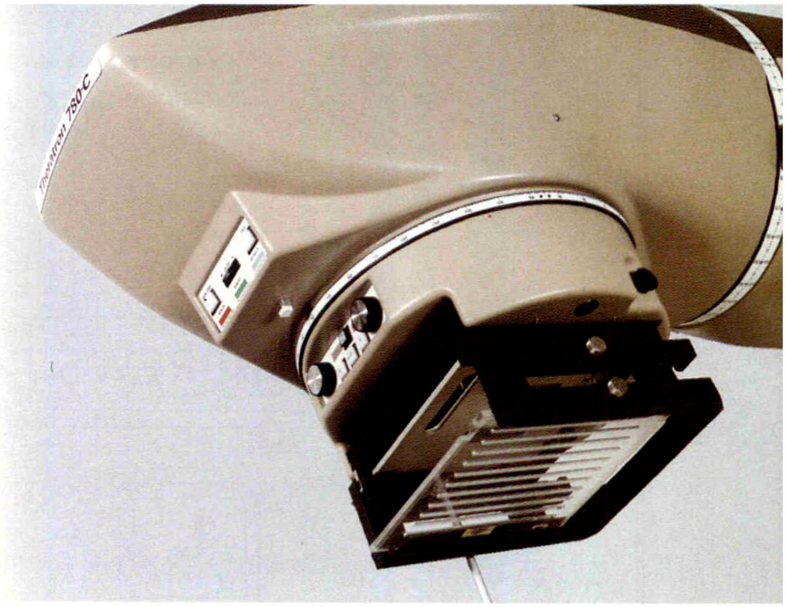

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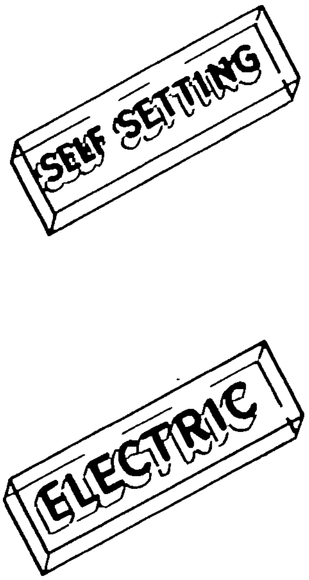

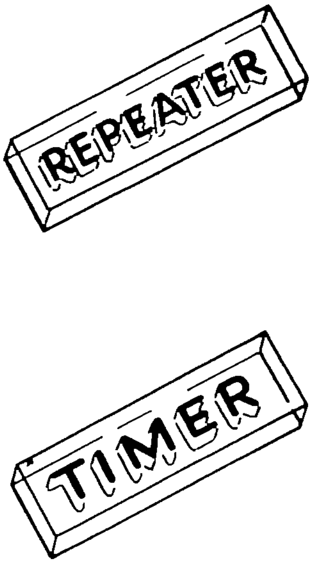

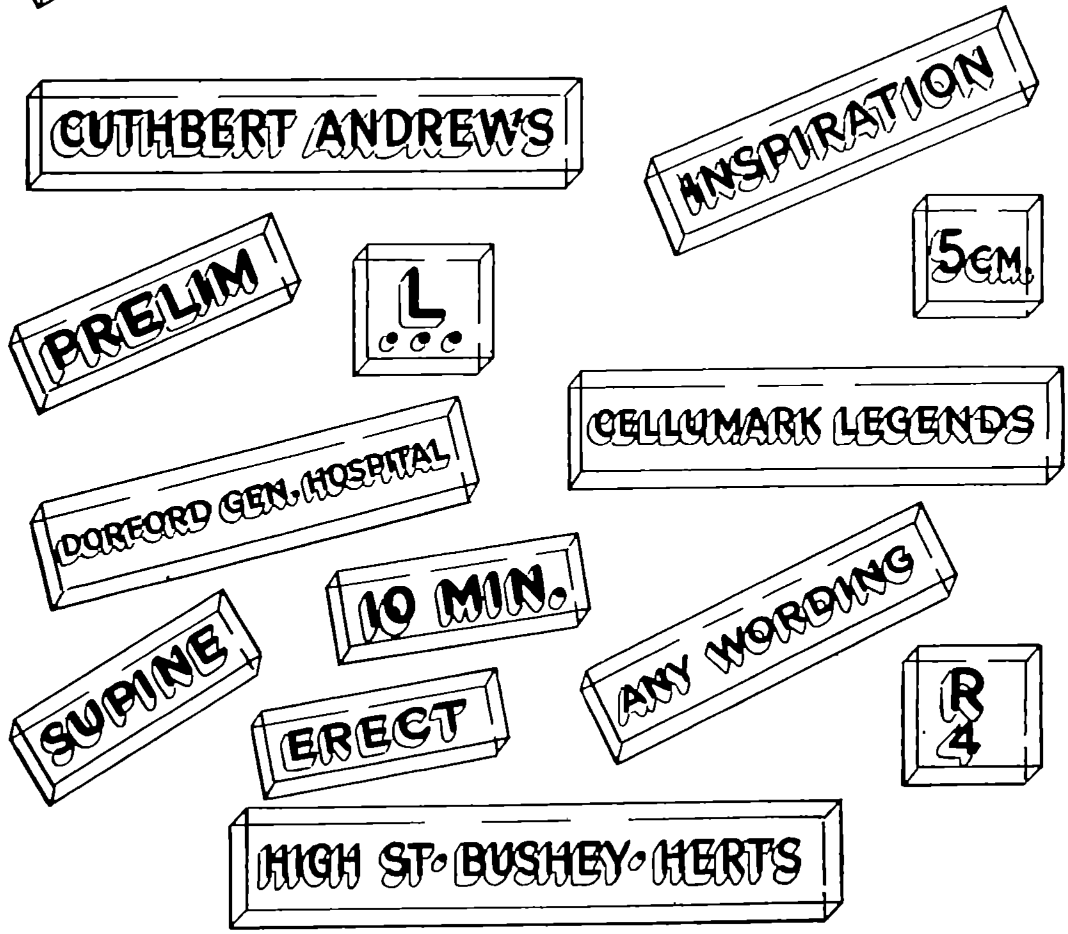

1986, *The British Journal of Radiology*, 59, 95

VOLUME 59 NUMBER 698 FEBRUARY 1986

The British Journal of Radiology

Editorial

The British Institute of Radiology traces its history back to the Roentgen Society founded in 1897, less than two years after the discovery of X rays. It can thus claim to be the first radiological society in the world. A distinctive feature of the Institute, one which it inherited from the Roentgen Society, is the multidisciplinary nature of its membership: diagnostic radiologists, radiotherapists, specialists in nuclear medicine, physicists, radiographers, engineers, radiobiologists and radiation chemists This journal is the official journal of the Institute, and the Editors have always been concerned to publish scientific articles that reflected the wide-ranging interests of the membership. This has sometimes meant that in any one issue of the Journal an individual reader may have found few articles directly related to his or her particular interest. This may have seemed particularly true for radiotherapists and radiobiologists, who might see the Journal as being predominantly of interest to diagnosticians. However, annual surveys over the years have shown that the proportion of published papers that are, for instance, specifically radiobiological in character has not decreased, and this has happened in spite of the increase in the number of specialist journals that have appeared.

We believe that the multidisciplinary nature of the Institute is one of its greatest strengths, and that this should be reflected in the editorial policy of the Journal. As Editors we are concerned that, if the Journal is to fulfill this policy adequately, it needs as strong an input of papers from radiotherapists and radiobiologists as from the other radiological disciplines. We therefore intend to publish a series of review articles on subjects of current interest in radiotherapy and radiobiology, and we also wish to make clear that papers in these disciplines are always welcome provided, of course, that they comply with our normal scientific standards. Furthermore, since the treatment of cancer is now such a multidisciplinary endeavour, we shall, in future, accept papers on topics in clinical oncology in its broadest sense, even though they may not have a specifically radiological content.

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J. T. Patton

Book reviews

Diagnostic Ultrasound of the Lower Abdomen. By A. Trenta, P. Pavlica, G. Stasi, R. Tonti, G. Vighetta, pp. 199, 1985 (Piccin/Butterworths, Italy), £39.00.
ISBN 0-407-01055-6

The authors' aim is to "define the potential and the limits of echography" in the lower abdomen. In this they have succeeded and managed to do so in a compact volume. The normal and pathological ultrasound appearances in the male and female pelvis are covered in the well established format of an introductory text followed by annotated illustrations. Coverage is comprehensive (obstetrics excepted), with several unlikely chapters, such as those on the appearances in the pelvis after recto-sigmoid excision and musculoskeletal tumours of pelvic origin, besides the expected gynaecological and urological applications. There is a section on scanning techniques, although the approaches using a static scanner are unlikely to be helpful in an age when most ultrasound is, rightly, based on real-time systems. The under-emphasis of the role of real-time systems is apparent within the text, with problems that are quickly solved on real-time, such as the observation of gut peristalsis, being laboured. The images are also mostly static, although their larger field of view makes them more easily understood and, therefore, acceptable in teaching. The image quality is satisfactory and the major features on each illustration are clearly labelled.

The text is rather cursory, the clinical introductions being brief and sometimes platitudinous. Oddities of translation have crept in with some quaint neologisms, for example, "lateroversion". There is yet another new meaning for "parameter", besides its general misuse in place of "variable", it now refers to tissues that lie beside the uterus. More regrettable is the absence of explanations of why the sonographic features illustrated are interpreted as particular pathologies, so that the beginner will not benefit fully from the case material. The coverage generally with a single example of each pathology, does not allow this to be considered as the definitive reference work in ultrasound of the pelvis.

In summary, a useful book to borrow and peruse.

DAVID O. COSGROVE

Ultrasound Annual 1984. Ed. by R. C. Sanders and M. C Hill, pp. ix+292, 1984 (Raven Press, New York), $52.00
ISBN 0-89004-579-8

This is the third in an annual series of books comprising 10 review articles, each of which is accompanied by very extensive reference lists. The choice of subjects is diverse and disconnected but aims to focus on new and innovative uses of ultrasound.

In general, the contributors seem to have been chosen well and have sound knowledge and experience in their allocated subjects. In this volume the chapters on fetal neurology, neonatal neurosonography and neonatal abdominal ultrasound are of particularly high quality and the chapter on ultrasound and scintigraphy of the biliary tract is interesting. The sections on sonography of fat, the placenta and on speech and swallowing are of less obvious value. The last chapter purports to be a statement of the "current state of thyroid ultrasound". Surprisingly, the majority of scans are taken with a manually operated static scanner and have reproduced in almost bistable mode. The contents of the chapter belie the title.

The general standard and technical adequacy of the scans illustrating the text is high and the reproductions are generally of very high quality, all but two of the images being black-on-white presentation.

The reviewer found much of interest in this volume and it will undoubtedly be a most useful bench book.

HYLTON B. MEIRE

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The combination of radiotherapy and surgery in the treatment of carcinoma of the uterine cervix

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ABSTRACT

In the Department of Radiotherapy and Oncology at Oxford, 1303 patients were registered between 1950 and 1975 with a diagnosis of carcinoma of the uterus, from these, 883 cases of carcinoma of the uterine cervix could be identified with certainty. Each patient's full clinical record was established from multiple hospital notes, operating theatre records, histopathological report files and so on. A uniform classification, based on the TNM system, was used for all patients. A data file, suitable for computer analysis, was established which contained all the available data. Analysis revealed that all patients could be divided into two distinct groups that had been prospectively determined and that the allocation achieved was random. The results, by various methods of analysis, show consistently that a policy of radical radiotherapy combined with radical surgery gave an increased survival rate, and a decreased mortality rate from cancer when compared with a treatment policy of only radical radiotherapy. During the 25 years being reviewed there was a progressive increase in the number of young patients with cancer of the uterine cervix in the early stages of disease at presentation and in the survival of patients with the early stages of invasive cancer.

The search for the optimum treatment of carcinoma of the uterine cervix continues and is associated with an unresolved controversy caused by the multifactorial nature of the problem. Fresh data often help to resolve problems that have already been identified but they may also help by challenging previously held strong convictions concerning methods of treatment, which in themselves may contribute little or no benefit to an individual patient.

Prior to the era of the prospective randomised clinical trial, records of past experience had always formed the foundations on which the future was built and on the basis of this philosophy a review was undertaken of the records of all patients registered in the Department of Radiotherapy and Oncology at Oxford from its inception in 1950 through to the beginning of 1975. A total of 1979 patients had a diagnosis of gynaecological cancer recorded at the time of registration, of whom 1303 had a diagnosis of carcinoma of the uterus and of these, the 883 patients in whom a specific diagnosis of carcinoma of the uterine cervix was finally established, were admitted to this study. Examination of these records revealed two groups of patients in whom treatment had differed significantly. The baseline variables in these two groups have been examined in detail and found to be similar without exception. The allocation of patients was through general practitioner randomisation and appears to satisfy the criterion of balance sought through the modern method of prospective random allocation, thus allowing a fair comparison between the treatment groups (Altman, 1984).

MATERIALS AND METHODS

Treatment policy

In the majority of patients it was possible for the radiotherapist and the gynaecologist to perform their critical assessment at a joint examination under anaesthetic. At this, a cystoscopy was performed initially and then a bimanual examination of the pelvis was undertaken, both per vaginam and per rectum. The staging of the disease was based on the physical signs if these were agreed but, if there was a difference of interpretation of the physical signs by the two examiners and this difference would have led to a difference in staging, then the lesser stage was accepted for the record. A dilatation and fractional curettage were performed and, when indicated, one or more biopsies were taken from the cervix or vagina. On occasions, a cone biopsy was deemed necessary. Colposcopy was not performed routinely, due to lack of adequate facilities over the years being studied. In all but a very few cases radiation sources were only inserted after histological confirmation of the invasive nature of the tumour had been obtained.

Patients with pre-invasive lesions, that is, carcinoma *in situ*, without breach of the basement membrane, as distinct from lesions where microinvasion was present, were treated entirely surgically. One treatment policy (Group I) was applied to patients with carcinoma of the cervix Stages IA, IB, IIA, IIB who were treated by two or three radium insertions, followed by a Wertheim hysterectomy and bilateral lymphadenectomy approximately 4 to 6 weeks later; subsequent external beam irradiation was given only when there was histological proof of malignant cells being present in the lateral pelvic wall lymph nodes. A histological report of residual tumour at the primary site was not acted upon, as it was felt that the viability of such a tumour could not be assessed histologically and, at any rate, the adjacent urinary bladder and the rectum had already received virtually their tolerance dose of irradiation from the radium insertions. Another group of patients (Group II), that were under the care of a gynaecologist who believed in radiotherapeutic treatment alone for this disease, had similar radiation treatment by radium and external irradiation to that given to the first group, but these patients did not have an operation. These two groups were divided by prospective randomisation through their general practitioner referring them to a particular gynaecologist, whose specific treatment policy for carcinoma of the cervix would not have been known to the large number of referring general practitioners involved in this study. The validity of this assumption is supported by the fact that, during the period of this review, the mortality from carcinoma of the cervix was only 90/million/year average and so each general practitioner would, on average, only see one new case of carcinoma of the cervix every other year whilst having reason to refer many patients with other diseases to any one of a number of gynaecologists annually.

Patients with carcinoma of the cervix Stages III or IV were deemed inoperable in the first instance and they were treated by irradiation only, often simply for relief of distressing symptoms. There was no fixed policy for the treatment of these patients and a variety of combinations of intracavitary and external beam irradiation were employed. Some of these patients were entered into the MRC trial of hyperbaric oxygen as an adjuvant to irradiation (Watson et al, 1978). In some of these patients the immediate radiation response was such that it became possible to offer them radical surgery, but pelvic exenteration has rarely been performed in Oxford. Salvage surgery for recurrent tumour activity has been performed on a number of occasions, but was based entirely on individual patient's needs, as there was no specific treatment policy.

In a few patients the disease was so advanced at the time of presentation that it was no longer possible either to identify the primary site of the malignancy with any degree of certainty, or to achieve any palliation through irradiation, and these patients were excluded from the study.

Staging and histological classification

The Department of Radiotherapy and Oncology has maintained its own records throughout the period of study but, because the Department acts as a regional centre, much of the vital information that was required for this review was contained in the gynaecological records at the referring hospital. It was necessary, therefore, to assemble the individual records for each patient so that all data could be cross-checked against the original entries, such as findings at examination under anaesthetic, operation records, histological reports and so on. Because of the major revisions that have occurred in the various staging systems over the 25-year period under review, it was considered essential to use the same criteria for allocating all the patients included in the study and so the original clinical findings were used to stage individual cases by the TNM system (International Union Against Cancer (UICC), 1978). A data sheet, suitably set out for later translation via a punch card, to a computer tape, was then completed with the relevant data for each patient. For the purposes of this review the date of entry into the study was taken as the date of the first treatment, whether that was by radiation or by surgery.

According to reports appearing in the literature, the terminology used for histopathological reporting has been a source of considerable controversy and appears to have varied widely over the period covered by this review (Brudenell et al, 1973). The terminology used by the pathologists in Oxford from 1950 to 1975, however, accords with that accepted for the latest revision of the TNM system (UICC, 1978) so that we have accepted cases into this study as having invasive cancer, if they would have been placed in Stage IB (UICC, 1978) and have placed cases that would now be classified as Stage IA (UICC, 1978) into the stage TIS (UICC, 1974), though, for clarity, these few patients with Stage TIS have been included with the Stage I cases when a previous separate analysis had shown that such an inclusion did not alter the quoted result or its statistical analysis.

All histological reports were classified into four groups: squamous-cell carcinoma; adenocarcinoma; undifferentiated carcinoma and a mixed group, in which were included all other specified forms of histological appearance, such as sarcoma, and those cases in whom the single word "carcinoma" was used in the report. In a large number of records, in which a diagnosis of squamous-cell carcinoma was given, there was also a note of the Broders grading, from I to IV, and these records have been analysed separately (Broders, 1925).

Intracavitary radiation techniques

Radium 226 has been the isotope used for all patients receiving intracavitary treatment with the exception of one case, where a vaginal mould was constructed and loaded with iridium-192 wires. Intracavitary irradiation with caesium-137 sources only commenced in the Department in Oxford in 1975 and no cases treated by caesium insertions are included in this study. In the period 1950–66 the intracavitary technique used was that described by Ellis & Oliver (1955). From 1967 onwards the intracavitary technique was changed to that developed by the author, which involved a much more versatile central source applicator with the facility for differential shielding and afterloading (Fleming & Wiernik, 1963; Bates et al, 1968; Stallworthy & Wiernik, 1976).

Our regime involved the use of two 25 mg radium tubes in tandem in the uterine cavity and two 25 mg radium tubes in the Ellis spreader (Ellis & Oliver, 1955). These radiation sources were inserted for 24 h on three occasions with 1-week interval between the first two insertions and a 2-week interval between the second and third insertions. A total radiation dose of 7200 mg h was then said to have been given. Over the years multiple attempts have been made to express this radiation dose in terms of modern units. It is the view of the author that all these attempts cannot be more than poor approximations to the true dose, because too little is known of the relative biological effectiveness of radiations given either as brachytherapy or as high-dose-rate teletherapy. The most up-to-date interpretation would suggest that this radiation dose of 7200 mg h approximates to 6600 cGy at a point which is referred to as the Manchester Point "A" (Tod & Meredith, 1938). An alternative regime was the application of the radium in the same physical distribution, but involving only two insertions, 14 days apart, for 30 h on each occasion which, therefore, gave a total dose of 6000 mg h.

Modifications were made for extension of tumour into the body of the uterus when three 25 mg radium tubes in tandem were used for a shorter period so that a similar total dose in mg h was achieved.

In order to obtain an immediate rough guide to the radiation dose in the individual patient, a probe counter was used to record the dose in the bladder and in the rectum. It has always been recognised that this method of assessment is open to criticism, due to the wide variations in reading that can be obtained by manipulation of the probe, but relatively consistent results are recorded in practice by trained staff. Possibly the greatest benefit from the probe measurements was that very high doses, well outside the normal range, were registered if the intrauterine source accidentally slipped down into the vagina during the packing procedure Such a misplacement could then be corrected immediately, and we believe that, in part, this accounts for the particularly low morbidity which has occurred.

A further check on the position of the radium was provided by immediate antero-posterior and lateral pelvic radiographs to show the configuration of the sources; these radiographs were also used for calculation of the dose from the radium for the planning of external beam irradiation.

Radiation protection for staff was achieved by bedside lead screens and by the use of single rooms for patients with loaded applicators, where the physical size of the rooms provided adequate distance to bring personnel doses down to acceptable levels.

External beam therapy

From 1950 to 1957 the external beam therapy was given with 250 kVp X rays, which were filtered to give 2 mm Cu HVL. The exact distribution of entry portals was determined by the size of the patient, but mostly two parallel opposed, anterior and posterior, 15 cm × 15 cm treatment portals gave an adequate dose distribution, though up to six portals had to be used in obese patients. A three-dimensional assessment of the position of the intracavitary sources, from the radiographs, was taken into consideration when planning the external beam therapy. A tumour dose, which was taken as the mid-plane dose, of 3000 cGy was given in 13 fractions over 28 days, that is, on a thrice-weekly basis. Lead blocks were used to shield the central area which had received the high dose from the intracavitary irradiation

From 1957 onwards, when a telecobalt machine was installed in the Department, all patients were given external beam therapy by parallel opposed antero-posterior fields with the cobalt beam. The fields used gave a 17 cm × 17 cm field at the mid-plane of the patient. The fields were applied in a diamond fashion with one corner of the field over the vulva; this allowed, firstly, both obturator foraminae to be included with the lateral pelvic walls of the true pelvis and, secondly, the field to extend up to the fifth lumbar vertebra so that the internal, external and common iliac nodes were included in the irradiation zone, but the majority of the femoral heads and necks on both sides were excluded. A similar irradiation technique was continued, but the tumour dose was raised to 3600 cGy given in 13 fractions over 28 days on a three fractions-per-week basis. It was considered that the biological effect of the treatment remained unchanged as the apparent increase in dose was compensated for by the change in RBE associated with the move from 250 kVp to megavoltage quality radiation and a change in units from roentgens (R) to rads (cGy), in which the dose was expressed.

In 1970 an 8 MeV linear accelerator was installed, and since that time the external beam therapy has been given by either of the megavoltage beams, as there was no material difference in the physical distributions. A central lead shield was used with this technique to cover all areas which had received a dose in excess of 6000 cGy from the intracavitary sources. The position of this isodose was calculated from the diagnostic pelvic radiographs taken as a check on the position of the radium sources immediately after each application; an average had to be derived because of the variation that occurred between the two or three separate insertions (Stallworthy & Wiernik, 1976).

Radical surgery

The radical surgical procedure practised in Oxford has been reported in detail by the gynaecologist who pioneered the combined approach at this centre (Stallworthy, 1964, 1967; Stallworthy & Wiernik, 1976; Stallworthy, 1981, 1984) but, with the passage of time, the majority of patients included in this study have been under the care of gynaecological colleagues. Details related to the surgical procedure are to be published elsewhere (Wiernik, 1986)

Follow-up

The majority of patients included in this study have been followed up regularly at joint clinics run by the radiotherapist and gynaecologist. It is our belief that the joint initial evaluation at the examination under anaesthetic associated with combined follow-up have contributed materially to our ability to combine radical irradiation protocols with radical surgery, so as to achieve the maximum obliteration of tumour with minimum morbidity. It has been possible to follow up the majority of patients for 10 years after their treatment, or until death. In a few instances we have had to rely on postal follow-up information.

Method of analysis

The raw data have been assembled so as to identify both the baseline variables which could have a prognostic importance, such as age of patient, stage of disease, method of treatment and pathological criteria, as well as other characteristics which, if not evenly balanced, could lead to bias, such as differences in cohorts of age groups, updating of equipment so that treatment facilities differed in subsequent quinquennia, changes in the pattern of causes of death and so on. The purpose of prospective randomisation in clinical trials of different treatments is to achieve a balance between groups to be compared so that there is the maximum likelihood that, if any difference is found, it will be due to the treatment being assessed rather than due to chance. Even prospective randomisation does not necessarily achieve this aim and invalidating bias may occur (Altman, 1984). Randomisation of patients in this study was based on a prospective, even if arbitrary, general practitioner referral system and not a prospective random-number allocation. In order to give confidence to the interpretation of the results, it must, therefore, be shown that the method of prospective randomisation that occurred in this study has not created a level of imbalance that is greater than could have resulted had the standard method of prospective random-number allocation been used. For this purpose, appropriate statistical tests have been applied to each of the variables with prognostic importance that are being considered and no evidence of undue imbalance has been demonstrated, so that the differences that have been found can, reasonably, be attributed to the efficacy of the individual treatment methods that are being compared.

The survival rates have been calculated by an actuarial method and the results given are the probabilities of a patient surviving to the end of each time period quoted; the standard error of that probability is also given.

For the purposes of this analysis the words "crude survival" refer to data that have not been corrected for the effect of age upon the percentage survival in different groups; the words "crude survival" are frequently used in the literature with reference to the completeness of the follow-up data but, as this analysis is based on an actuarial method, all the available data are used and the completeness of follow-up becomes irrelevant.

RESULTS

Whole-group classification

It is believed that all patients with a diagnosis of invasive carcinoma of the uterine cervix, who were resident in the wide geographical region served by the Department of Radiotherapy & Oncology at Oxford, were referred to the Department for consultation even though eventually, in a few patients, no form of irradiation played a role in their treatment. This was not the case when the diagnosis was one of *in-situ* carcinoma of the cervix, as these patients were mostly treated by surgery alone and so were never registered in the Department of Radiotherapy & Oncology. They are therefore not included in this study.

For a number of different administrative reasons there were material changes in staffing and treatment policy after 1970, so that the accession of new cases between 1970 and 1974 was not directly comparable with previous quinquennia, though the follow-up of cases treated in the earlier period continued without interruption to the end of the study period.

Treatment policy

The gynaecological surgeons working in the Oxford hospitals and those who had their practice in the surrounding region all shared a single Department of Radiotherapy & Oncology in Oxford, but there was a division of opinion as to whether radical surgery should or should not be combined with the radiotherapeutic treatment that was common to both groups. Group I, in which the initial intracavitary radium therapy was followed by radical surgery, included 770 patients (Table I) who had a statistically significant improvement in 5-year survival rate ($0.025 > p > 0.01$), when compared with Group II patients, who were treated entirely by intracavitary radium and external pelvic irradiation. The 10-year survival figures show that this improved rate in Group I has been maintained ($0.05 > p > 0.025$) The 5-year crude survival rate for all the patients included in the study was 51.3%, with a 10-year crude survival rate of 40.8%.

Variables with prognostic importance

Age. Analysis of the distribution of the ages of patients in Groups I and II shows that there is an even balance between both groups at all ages (Table II).

There is a close correlation between age and cause of

TABLE I

INCIDENCE AND CRUDE SURVIVAL RELATED TO TREATMENT POLICY

Group	No. of patients	% incidence ±SE	% 5-year survival±SE	% 10-year survival±SE
I	770	87.2±1.1	52.9±1.8	42.1±2.0
II	113	12.8±1.1	40.5±4.7	31.7±4.6
Total	883	100	51.3±1.7	40.8±1.8

TABLE II

INCIDENCE OF AGE AND STAGE RELATED TO TREATMENT POLICY

Group	Age								Total No.
	<39 years		40–59 years		>60 years		Not known		
	No.	% incidence ±SE	No.	% incidence ±SE	No.	% incidence ±SE	No.	% incidence ±SE	
I	115	14.9±1.3	411	53.4±1.8	241	31.3±1.7	3	0.4±0.2	770
II	11	9.7±2.8	60	53.1±4.7	41	36.3±4.5	1	0.9±0.9	113

	Stage										
	I		II		III		IV		Not known		
	No.	% incidence ±SE	No.	% incidence ±SE	No.	% incidence ±SE	No.	% incidence ±SE	No.	% incidence ±SE	
I	300	39.0±1.8	214	27.8±1.6	132	17.1±1.4	79	10.3±1.1	45	5.8±0.8	770
II	34	30.1±4.3	36	31.9±4.4	23	20.4±3.8	14	12.3±3.1	6	5.3±2.1	113

death that has been analysed in Table III, from which it can be seen that there is a significant increase ($p < 0.001$) in deaths due to cancer, in the older age groups when compared with the youngest age group, as well as for deaths not due to cancer where there is a significant rise in death rate ($p < 0.001$) between the youngest and the middle age group and between the middle and oldest age group ($0.01 > p > 0.001$).

In direct contrast to the incidence data, the mortality data for those dying from cancer show a remarkable uniformity between the three age groups, *i.e.* just over 90% of such deaths occurring within 5 years.

The combination of the increased mortality from cancer, in the oldest age group, with their generally increasing death rate from other causes, gives rise to a highly significant diminution in the percentage of patients alive over the age of 60 years. This finding is contrary to that of other recent reports (Roberts, 1982; Paterson et al, 1984) and may reflect a changing pattern of disease in the last decade. In Table III, as in the whole of this study, for the sake of clarity, the group designated as "alive" contains all those patients whose records did not show evidence of death having occurred prior to or at the time of assessment. No attempt has been made to check this fact, for individual patients, with the Office of Population Censuses and Surveys.

When incidence and survival were analysed in relation to age no significant differences were found between the patients in Group I and those in Group II.

Stage. The incidence and 5-year crude survival data have been analysed by subdivision into the TNM Staging (UICC, 1978) (Tables II and IV). The survival rate in all Stage I cases is significantly better than that in Stage II cases ($p < 0.001$) which, in turn, is significantly better than the survival of patients with Stage III or Stage IV disease ($p < 0.001$); there appears to be a greater survival rate in Stage III compared with Stage IV, but this does not reach a level of significance

Quinquennial analysis shows an overall variable pattern without any definite trend being apparent within each stage grouping and this dictates caution in the interpretation of statistically significant differences ($p < 0.001$) between individual subgroups as, for example, in either Stage I percentage incidence between

TABLE III

INCIDENCE AND MORTALITY AT 5 YEARS: AGE RELATED TO CAUSE OF DEATH

Cause of death	Age								
	<44 years			45–59 years			>60 years		
	No.	% incidence ±SE	% mortality ±SE	No.	% incidence ±SE	% mortality ±SE	No.	% incidence ±SE	% mortality. ±SE
Cancer	82	20.0±2.0	90.2±3.3	158	38.4±2.4	91.1±2.3	171	41.6±2.4	91.8±2.1
Not cancer	9	9.5±3.0	66.7±15.7	33	34.7±4.9	37.0±8.5	53	55.8±5.1	48.2±6.9
Alive	160	42.4±2.5	—	157	41.6±2.5	—	60	15.9±1.9	—

TABLE IV

INCIDENCE AND 5-YEAR CRUDE SURVIVAL: STAGE RELATED TO QUINQUENNIUM

Quinquennium	No.	% incidence ±SE	% survival ±SE
Stage I			
1950–54	35	24.6±3.6	77.0±7.1
1955–59	67	40.6±3.8	64.7±5.9
1960–64	89	36.3±3.1	73.0±4.7
1965–69	123	44.9±3.0	87.4±3.2
1970–74	20	35.1±6.3	68.9±10.6
Stage II			
1950–54	45	31.7±3.9	53.3±7.4
1955–59	47	28.5±3.5	53.1±7.3
1960–64	83	33.9±3.0	53.7±5.5
1965–69	63	23.0±2.5	50.3±6.5
1970–74	12	21.1±5.4	37.1±15.0
Stage III			
1950–54	33	23.2±3.5	27.3±7.8
1955–59	30	18.2±3.0	20.0±7.3
1960–64	29	11.8±2.1	24.1±7.9
1965–69	46	16.8±2.3	15.0±5.3
1970–74	17	29.8±6.1	0
Stage IV			
1950–54	15	10.6±2.6	0
1955–59	14	8.5±2.2	31.5±12.9
1960–64	34	13.9±2.2	11.8±5.5
1965–69	26	9.5±1.8	11.0±6.3
1970–74	4	7.0±3.4	0
Not known			
1950–54	14	9.9±2.5	63.2±13.2
1955–59	7	4.2±1.6	57.1±18.7
1960–64	10	4.1±1.3	30.0±14.5
1965–69	16	5.8±1.4	57.0±13.7
1970–74	4	7.0±3.4	0

1950–54 and 1965–69 or in percentage survival between 1955–59 and 1965–69 (Table IV).

Histology. It will be seen from Table V that nearly three-quarters of the patients in this study had squamous-cell carcinoma of the cervix and that 10% had an adenocarcinoma. The 5- and 10-year crude survival rates for these different histological types can be seen not to differ significantly at either point of analysis. The Broders grade (Broders, 1925) was available for the majority of patients and has been analysed in relation to treatment policy (Table VI). The incidence figures confirm the even balance achieved by the general practitioner randomisation while the survival figures show no significant association with the degree of differentiation identified by applying the method of Broders grading.

Treatment. The difference between the patients in Groups I and II was the method of treatment to which they were prospectively allocated and analysis of the results shows a significant advantage for those in Group I (Table I). It was not appropriate, however, to treat every patient in an exactly similar manner and so a number of subgroups, based on the actual method of treatment employed, can be identified but in the majority of these the number of patients that are included in individual subgroups are too small to allow for reliable analysis.

An apparently significant difference between patients treated with two or three radium insertions has been noted but as this is likely to be directly related to the dose of radiation that each subgroup received it is considered that further analyses of these factors should be performed and these will be published elsewhere if found to be contributory.

Cause of death. The relationship between the age of the patient and the cause of death has already been analysed (Table III). Added analyses, both by stage and treatment policy, have been performed and, in summary, show a significant difference in favour of Group I ($0.025 > p > 0.01$) when the deaths from cancer in all stages taken together are compared between Groups I and II.

DISCUSSION

Radiotherapy versus surgery

Much time and effort has been contributed by radiotherapists and gynaecologists addressing themselves to the problem of the best therapeutic regime for patients suffering from carcinoma of the uterine cervix. Review of the world literature has revealed such marked differences in the survival rates of patients

TABLE V

INCIDENCE AND CRUDE SURVIVAL RELATED TO HISTOLOGY

Histology	No. of patients	% incidence ±SE	% 5-year survival±SE	% 10-year survival±SE
Squamous-cell carcinoma	646	73.2±1.5	50.2±2.0	40.5±2.1
Adenocarcinoma	92	10.4±1.0	45.9±5.4	32.8±5.7
Undifferentiated carcinoma	15	1.7±0.4	38.9±12.9	30.2±12.6
Carcinoma *in situ*, other histology, not known	130	14.7±1.2	62.3±4.4	48.6±5.1
Total	883	100	51.3±1.7	40.8±1.8

TABLE VI

INCIDENCE AND 5-YEAR CRUDE SURVIVAL. BRODERS GRADE RELATED TO TREATMENT POLICY

Broders grade	Group I			Group II		
	No	% incidence ±SE	% survival ±SE	No.	% incidence ±SE	% survival ±SE
I	44	5.7±0.8	58.6±7.8	3	2.7±1.5	66.7±27.2
II	201	26.1±1.6	49.3±3.6	38	33.6±4.4	40.6±8.1
III	244	31.7±1.7	49.6±3.3	34	30.1±4.3	40.0±8.5
IV	95	12.3±1.2	40.5±5.2	16	14.2±3.3	43.8±12.4
Not known	186	24.2±1.5	66.3±3.6	22	19.5±3.7	34.2±10.5

treated by apparently similar regimes that genuine doubt remains concerning the cause of any differences that have been found, and especially the attribution of such differences to one or other method of treatment (Blaikley et al, 1969). It would appear that the best hope of resolving this problem depends upon obtaining the results of a controlled clinical trial where such factors as pre-randomisation losses (Charlson & Horwitz, 1984), problems associated with historical control groups, geographical distribution, ethnic origin, etc., do not cloud the issue as to whether one method of treatment achieves better results than another. In theory, a large clinical trial based on classical prospective randomisation is called for but, so far, the results of such a trial do not appear to have been published and such a trial is unlikely to be undertaken at this juncture for practical reasons (Freedman, 1985). A detailed statistical analysis of the results of treatment in Oxford, that has often been called for (Blaikley et al, 1969), has been undertaken and this has revealed data that show that a form of prospective randomisation had taken place, without it being recognised as such at the time, which now allows reliable comparison to be made between methods of treatment of carcinoma of the cervix either by a combination of radical radiotherapy with radical surgery, or similar radical radiotherapy alone. Statistical assessment of the data confirms that Groups I and II can be reliably compared as all the patients known to have been treated during the period under review can be allocated to one of the two groups which were determined prior to any patient being allocated to either of them. The present study is, therefore, not a subgroup analysis, nor does it carry any of the undesirable stigmas of what is loosely termed "retrospective" analysis for, when all is said and done, the analysis of any trial must "a priori" be carried out retrospectively. The most serious statistical concern is with the skew distribution of the total number of patients caused by the 7:1 allocation to Groups I and II, evidence that this has not led to any undue bias has been established by the even balance between patients that has been found in all subgroup analyses when these have not been perturbated by the direct effects of the policy difference between Groups I and II The data presented in this respect are, therefore, consistent throughout the analysis and so do not represent extreme treatment differences between subgroups that have attracted attention (Freedman, 1985).

Further support comes from comparison of the results obtained in Group II, the patients treated by radiotherapy alone, with the series treated in a similar manner, over the same time period, in a neighbouring region (Jolles, 1980). These data are remarkably similar and are consistent with a treatment policy of radiotherapy and surgery, in both centres, achieving significantly better results. Comparison with other recently published data on the treatment of carcinoma of the cervix (Mould & Staffurth, 1979, Mitchell et al, 1980; Brand & Kerr, 1982) is of interest and confirms similar trends to those identified in this study, but such comparisons do not contribute any more now than similar attempts have done in the past to the most important issue, namely, that of how to improve treatment methods so as to achieve an increased survival of patients.

Among the criticisms of the Oxford data in the past (Stallworthy, 1967) has been that the results appeared to depend on the expertise of a single surgeon, but the present report is based on the contribution of more than a dozen surgeons operating at their own hospitals, and a subgroup analysis of results, by individual surgeon, showed no material difference between them. Complications arising from the combination of radical surgery with radical radiotherapy, such as fistulae, oedema, etc., are frequently attributed to the surgical element of the treatment, but comparison of Groups I and II does not support such a contention (Wiernik, 1986).

Variables with prognostic importance

Age. We have noted a significant increase, between 1950 and 1970, in the percentage of patients in the youngest age group (Wiernik, 1986) which is similar to the findings by Mitchell et al (1980). We have also noted an increased incidence of earlier stages in the younger age groups which accords with the findings of Brand and Kerr (1982). There was no evidence in our study of the frequently quoted belief that the virulence of malignancy is greater in the youngest age group because the length of survival of patients who did die from their cancer was similar in all three age groups (Table III).

Stage. The increased percentage incidence in Stage I cases between the quinquennia 1950–54 and 1965–69 (Table IV) is not at the expense of only Stage II cases as reported from another centre for the same time period (Mitchell et al, 1980), for our combined Stage I and Stage II incidence still shows a significant ($0.025 > p > 0.01$) increase over the period 1950–69 and it would appear that at our centre there has been an overall change in favour of patients presenting at an earlier age with an earlier stage of the disease. Our data are consistent with the thesis that the natural history of cancer of the cervix starts in young women and then progresses slowly and inexorably over the years so that those in the oldest age group present with the most advanced disease. We have no evidence that the cancerous process is any more aggressive in those in the older age group, accounting for the late stage of the disease on presentation, as the mortality at 5 years after treatment for those dying of cancer is the same in the oldest and youngest age groups (Table III). Our data do not, however, contribute to the relationship that invasive cancer bears to the pre-malignant phase as the 16 patients with Stage TIS which we have included in this study, are grossly unrepresentative of the incidence of this phase of the disease during the 1950–75 era. Furthermore, because of the changes in the referral pattern after 1970, no confident assessment can be made as to whether the natural history of carcinoma of the cervix, especially in the youngest age group, has or has not altered in recent years in the population which we serve (Paterson et al, 1984).

Histology. Attention has been drawn to the exact composition of our Stage I subgroup, which contained 16 patients in whom the histological diagnosis was one of microinvasion. Thirteen of the 16 patients had a radical operation and in none of these patients were the lateral pelvic wall lymph nodes found to contain tumour. There were no deaths out to 10 years in these patients. It has often been held that a reader's inability to identify the size of this particular group, with such a good prognosis, within the general Stage I classification, accounts for certain authors achieving apparently better results when using otherwise similar methods of treatment.

The incidence of adenocarcinoma in our series at 10.4±1.0% (Table V) appears to be more in line with other recent reports of patients treated over the same time period (Blaikley et al, 1969; Mould & Staffurth, 1979) than with the incidence of 3.8% reported by our neighbouring centre (Jolles, 1980), but this is regarded as being of little significance in view of the small total numbers involved. Hearsay always attributes a worse prognosis to patients suffering from an adenocarcinoma of the uterine cervix when treated by radiotherapy alone, and this is frequently quoted in defence of a policy of treating these patients surgically. It is, therefore, of interest that no significant difference was found in our series, in the 5- or 10-year crude survival rates, when all patients with adenocarcinoma were compared with patients with squamous-cell carcinoma (Table V); neither was there a difference when these two groups were compared by treatment policy (Group I vs Group II), nor when they were compared by creating further subgroups by division into individual stages.

The failure of the Broders system of grading (Broders, 1925) (Table VI) to correlate with prognosis is also of interest, because it confirms the views of Willis (1948). One of the possible explanations is that the Broders grading is based on the average degree of differentiation observed by the pathologist, whereas prognosis is likely to be related to the least differentiated portion of the whole tumour that will not necessarily have been included in the histological sections used for the determination of the grading. These findings support our lack of confidence in histological reports forming the basis of advice regarding the suitability of treatment by either radiotherapy or surgery and they concur with other centres (Blaikley et al, 1969).

Treatment. When we considered the results of other treatment regimes that were employed during the course of this study but which differed from those that formed the basis of the random allocation into Group I or II, a number of factors had to be borne in mind: caution in interpretation was called for, as some of the different methods, such as external radiation only, represented small subgroups that were not determined by prospective allocation and even one of the larger of these subgroups, "Radium and External Irradiation", was a composite group of patients treated in that manner either because of the prospective policy decision or because, in the particular patient, the policy decision of irradiation and surgery could not be applied as, for instance, in Stage III and Stage IV cases, so that the percentage survival in such a subgroup was biased.

A reasonably fair comparison, however, could be made between the 300 patients with Stage I disease in Group I and the 34 patients with Stage I disease in Group II, the 5-year crude survival in the former group was 78.0±2.5% and in the latter group 60.6±8.5% ($p < 0.05$), the difference rising at 10 years ($0.05 > p > 0.025$) (Wiernik, 1986). Furthermore, it was of interest to note that there was no difference in percentage survival between Groups I and II for patients with Stages III and IV disease who were treated in a similar manner in both groups.

CONCLUSIONS

The evidence presented allows the conclusion that a form, even if not standard, of prospective randomisation took place between a treatment group for carcinoma of the uterine cervix involving radical radiotherapy combined with radical surgery and a similar group treated by radical radiotherapy alone. Where valid comparisons can be made between the two groups, the former shows consistently better crude survival rates than the latter, mostly at significant statistical levels, at both 5- and 10-year follow-up periods. This conclusion is supported by the general trend in various forms of analysis of the complete data and is not based on a finding in a single subgroup that happens to show an extreme treatment difference. The policy of radical surgery in combination with radical radiotherapy, for suitable patients, shows a decreased mortality from cancer with no detriment from an increased morbidity despite the operative procedure being carried out by a number of gynaecological surgeons working in a variety of hospital facilities.

During the period under review, 1950–75, there was a significantly increased mortality from cancer in women over 60 years when compared with women under the age of 44 years, in addition to the anticipated significant increase in mortality from causes other than cancer. Similarly, our data confirmed the predictable significant increase in mortality with increasingly advanced stages of the disease at the time of presentation. Neither histological cell type nor Broders grading of differentiation of each tumour was found to be a useful guide to prognosis in individual patients

ACKNOWLEDGMENTS

I am particularly indebted to Professor Sir John Stallworthy and Dr Frank Ellis, who initiated this work in Oxford, but also to the large number of gynaecologists and my radiotherapeutic colleagues who have all participated in the day-to-day care and treatment of the patients, to Margaret Norris, whose devoted and unstinting efforts located the many hospital records of each individual patient and who completed most of the data sheets; to Julian Peto, who wrote the original computer program for analysis of the data and to Dr Yvonne Gunn, who continued with the analysis and has provided the statistical advice for me. Finally, I would like to thank the innumerable other kind persons who have contributed their labours so generously, as without them this study would not have been possible, and especially Mrs Lynn Pilling, my secretary, who typed the manuscript as well as gathering a great volume of information

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Correction

Spinal cord compression in Léri's pleonosteosis. By R A. Metcalfe and P. Butler. *British Journal of Radiology* (1985), *58*, 1117–1119.

We must apologise for the fact that the authors' addresses were accidentally omitted from this paper in the November issue of the Journal. Drs Metcalfe and Butler are at the Departments of Neurology and Neuroradiology, respectively, Manchester Royal Infirmary, Oxford Road, Manchester.

Would readers please correct their copies?

Book review

Angiographic Diagnosis of Supratentorial Cerebral Tumours (Compared With CT Scan). By A. Pansini and P. Conti, pp. 280, 1984 (Piccin Nuova Libraria, Padua), Lire 80 000.
ISBN 88–299–0083–4

The title of this book does not give a true indication of its contents since comparison between the two diagnostic procedures occupies little more than 20 pages. In effect, it is an attempt to promote angiography and there can be little purpose in this exercise since the topic has been more than adequately covered elsewhere. The quality of the angiograms is frequently rather poor and many anatomical errors are present.

The text is particularly difficult to follow, both because of the use of Italianised words and because the language is verbose. It would appear that the English is a direct translation of the original Italian and, frequently, it is unintelligible.

I can see little purpose in recommending this book to students with little experience of neuroscience because of the many inaccuracies. Those who are advocates of cerebral angiography will have little need for it and for those who need a reference work on angiography there are many other and better works.

DEREK KINGSLEY

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A clinical phase I toxicity study of Ro 03-8799: plasma, urine, tumour and normal brain pharmacokinetics

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ABSTRACT

Ro 03-8799 is a lipophilic, basic 2-nitroimidazole of greater potency than misonidazole, which we have administered to 52 patients The dose-limiting toxicity is an acute central nervous system toxicity with symptoms which include nausea, disorientation, sweating, a feeling of heat and, in one extreme case, coma. Pharmacokinetic analysis was carried out in 31 patients. The mean distribution phase half-life was 44 min and the mean elimination half-life was 6.1 h Peak concentration was linearly related to dose over the range 0.25 g/m² to 3 g/m² with a mean at 1 g/m² of 15.7 μg/ml. Area under the curve was also linearly related to dose and the average whole body clearance was 20.1 l/h. Urinary recovery at 24 h was 31% for the parent compound and 28% for the N-oxide metabolite The drug is concentrated in normal brain, brain tumour and non-brain tumour to a similar extent, the respective mean tissue/plasma ratios being 381%, 329% and 355%. For a dose of 1 g/m², tumour concentrations were 1.5 times as high as for misonidazole, and the available *in vivo* and *in vitro* sensitisation data predict an improvement of 1.8 and 3.3 times respectively

Nitroimidazoles have proved effective radiation sensitisers of hypoxic tumour cells in a variety of experimental systems, but clinical results to date have been less successful Metronidazole, the first nitroimidazole to be investigated clinically as a hypoxic cell sensitiser, eventually proved disappointing (Urtasun et al, 1982) despite encouraging initial results (Deutsch et al, 1975; Urtasun et al, 1976).

In a decade of clinical trials, misonidazole (MISO) has been extensively investigated. Peripheral neuropathy has limited the total cumulative dose which can be administered (Dische et al, 1977). Possibly because of this dose limitation, only five clinical trials (Busutti, 1982; Mäntylä et al, 1982; Overgaard et al, 1982, Sealy & Cridland, 1984; Kogelnik et al, 1981) of a total of more than 30 so far reported have demonstrated any benefit associated with its use. In a recent update of the results of the first of these five, the advantage was no longer apparent (Stadler et al, 1984).

Peripheral neuropathy has also proved dose-limiting for those hydrophilic analogues of MISO (Dische et al, 1981; Coleman et al, 1982, 1984). While clinical work with desmethylmisonidazole has been discontinued, SR-2508 continues to show promise (Coleman et al, 1984)

Ro 03-8799 is a lipophilic 2-nitroimidazole with a basic side-chain and a somewhat higher electron affinity than MISO (Smithen et al, 1980). It was predicted that its basicity would enhance its excretion in acid urine, leading to a shorter elimination half-life and reduced normal tissue exposure (Wardman, 1979). It was further hoped that its basicity might lead to concentration in areas of low pH such as are commonly thought to occur in tumours. This, together with its higher electron affinity, would be expected to confer greater potency than MISO.

Experimental work *in vitro* (Smithen et al, 1980) and *in vivo* (Williams et al, 1982a) suggested that Ro 03-8799 might indeed have greater potency. Preliminary human studies using single small doses of the drug produced no drug-related toxicity, and tumour concentrations three times greater than in plasma sampled at the same time were obtained (Saunders et al, 1982). This accumulation within tumour tissue has been confirmed at higher doses (Saunders et al, 1984; Roberts et al, 1984). We now report clinical toxicity data, together with plasma, tumour and normal brain pharmacokinetics obtained in 52 patients during a Phase I assessment of the drug.

MATERIALS AND METHODS

Patients

Three groups of patients were given the drug. The first group consisted of patients with various histological types of malignancy given Ro 03-8799 as part of single dose and multiple dose escalating dose toxicity studies. The second group had accessible tumours that could be biopsied, and were given single doses of Ro 03-8799 prior to single or multiple biopsies of their tumours to provide samples for estimation of tumour concentrations of Ro 03-8799. The third group of patients had primary or secondary brain tumours and were given single doses of Ro 03-8799 prior to neurosurgical removal or biopsy of the tumours, again to allow estimations of tumour concentrations of the drug.

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In all cases patients had normal hepatic and renal function and were excluded from the study if taking corticosteroids or drugs known to induce hepatic microsomal enzymes.

All patients gave informed consent to inclusion in the study, which was approved by the local ethical committee.

Drug

Ro 03-8799 (2-nitro-α-(piperidinomethyl)-1-imidazole-ethanol hydrochloride) was provided by Dr I. Lenox-Smith of Roche, Welwyn, as a freeze-dried preparation of the hydrochloride salt. Single doses ⩽ 1 g/m^2 were dissolved in sterile water to give a concentration of 1 g/10 ml which was then made up to a total volume of 50 ml with physiological saline and administered intravenously as either a slow injection or an infusion over at least 10 min. Single doses > 1 g/m^2 and all doses for patients in the multiple dose toxicity study were dissolved in sterile water to give a concentration of 1 g/10 ml which was then made up to a total volume of 100 ml with physiological saline and infused using a calibrated intravenous infusion set.

All doses reported in this study correspond to the hydrochloride salt, whereas all plasma, urine and tumour pharmacokinetic data refer to the base.

Blood and tissue samples

Venous blood was collected via an indwelling cannula from the arm opposite the infusion. Samples were taken immediately before and at intervals of 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h from the end of the infusion. Blood samples were placed on ice or refrigerated at 4°C until separated. Plasma was then frozen to −20°C to await analysis. Tumour and normal tissue samples were placed, in sealed tubes, immediately into CO$_2$ ice for a short period and subsequently stored at −70°C to await analysis. They were thawed and processed on ice. Analysis of plasma, tumour and normal brain levels of Ro 03-8799 and its N-oxide metabolite Ro 31-0313 was performed by reverse-phase high performance liquid chromatography (HPLC) as described previously (Malcolm et al, 1983) with minor modifications (Walton and Workman, unpublished).

Ro 03-8799 plasma data were fitted to the standard equations for the 1- or 2-compartment model (Wagner, 1975), by non-linear regression analysis using Subroutine VC05AD of the Harwell Subroutine Library. Pharmacokinetic parameters were derived from standard equations (Wagner, 1975). Other regression analyses were carried out using the Generalised Linear Interactive Modelling Programme (GLIM) of the Royal Statistical Society of London

RESULTS

Toxicity

Single dose. In all, 22 patients were given single doses of 1 g/m^2 Ro 03-8799, either prior to biopsy of accessible lesions (11 patients), prior to neurosurgical removal or biopsy of brain tumours (nine patients), or as part of a single-dose, escalating dose toxicity study (two patients). The drug was administered to four of the brain tumour patients under a general anaesthetic for neurosurgery; the remaining patients were conscious during administration. One patient reported nausea during the infusion, and one felt light-headed. The remainder reported either a subjective feeling of heat, particularly around the face, or a chemical taste, or both. Our results for the single-dose escalating dose toxicity study have been published elsewhere (Roberts et al, 1984).

Both patients given a single dose of 2 g/m^2 reported feeling hot during the infusion, and also complained of paraesthesiae in the hand on the same side as the infusion. One patient described a strange sensation in the ears and was profoundly nauseated, vomiting 1.5 h after the end of the infusion.

The single patient given a dose of 3 g/m^2 (total dose 4.95 g) developed a dramatic acute toxicity syndrome. During the infusion he reported a feeling of heat, which was accompanied by facial flushing and profuse sweating. Paraesthesiae were reported, first in the hand on the same side as the intravenous infusion, and subsequently in all four extremities. At the end of the infusion the patient reported that his vision was obscured by a "purple haze". This was accompanied by angor animi. He vomited once then passed into coma. The tendon reflexes were slightly depressed, both plantar responses were flexor and the pupils responded normally to light. Coma lasted for 1.75 h. Thereafter he suffered from nausea and anorexia which lasted for 4 days, following which he made a complete recovery to pre-treatment status.

Multiple dose. Twenty-seven patients were given multiple, thrice weekly doses of Ro 03-8799 in an escalating dose toxicity study. Nineteen patients were entered into a 3-week escalating dose study and were prescribed nine doses of between 0.25 g/m^2 and 1 g/m^2 of Ro 03-8799. The drug dose was escalated on a group-by-group basis, each individual patient receiving the same dose on each occasion. No patient prescribed doses of 1 g/m^2 × 9 or less refused to continue with the drug. Two patients prescribed 0.25 g/m^2 × 9 had Ro 03-8799 discontinued after eight doses. In one case this was because of a spurious report of neutropenia, in the other because of headaches which were subsequently established as being due to cerebral metastases. One patient prescribed 0.5 g/m^2 × 9 doses had all treatment suspended after four doses because of very rapid progression of metastatic disease

All four patients prescribed 1 g/m^2 × 9 completed treatment as prescribed. A further escalation of dose to 1 3 g/m^2 × 9 doses resulted in two of the four refusing to continue beyond three and six doses, respectively, because of malaise and nausea.

Following this, the dose was returned to 1 g/m^2. Of five patients prescribed a total of 1 g/m^2 × 12 over 4

TABLE I

MULTIPLE DOSE SYMPTOMATIC TOXICITY

Dose g/m² × no. of doses	No. entered	Heat + sweating	Paraesthesiae	Disorientation	Chemical taste	Rash	Anorexia, nausea	Refused
0.25 × 9	3	0	0	0	0	0	1	0
0.5 × 9	4	4	0	0	0	1	2	0
0.75 × 9	4	2	1	1	2	0	1	0
1.0 × 9	3	3	1	1	3	0	3	0
1.3 × 9	5	4	0	2	2	2	3	2
1.0 × 12	5	0	1	3	0	1	4	2
1.0 × 15	3	0	0	3	1	1	3	2
Totals	27	13 (48%)	3 (11%)	10 (37%)	8 (30%)	5 (19%)	17 (63%)	6 (22%)

weeks, three completed treatment; two others refused to continue beyond one and nine doses, respectively. Of the three patients prescribed 1 g/m² × 15 doses over 5 weeks, two refused to continue beyond 12 doses because of progressively worsening malaise and anorexia. The third patient continued to the prescribed total dose of 15 g/m² despite obviously distressing side-effects.

The side-effects experienced by patients in the multiple dose study are summarised in Table I.

A feeling of heat and/or sweating was experienced by 13 out of 27 (48%) patients. It was not reported by any patient receiving 0.25 g/m² × 9 but otherwise does not seem to have been dose-related. Three patients (11%), all of whom received individual doses > 0.75 g/m², complained of paraesthesiae in the hand into which the Ro 03-8799 was infused. These lasted only as long as the infusion and were in no case distressing. Ten of 27 patients (37%) experienced a sense of disorientation or detachment during, or shortly after, infusion of the drug. This sensation was difficult for patients to describe accurately. It was variable, in that a given patient might experience it with some, but not all doses of the drug, and the degree of distress caused seemed to vary both from patient to patient and from dose to dose for any given patient. It was not reported with doses below 0.75 g/m². None of the patients in the multiple dose study experienced any disturbance in consciousness.

In eight cases (30%) patients complained of an unpleasant "chemical" taste during infusion of the drug. Again this was not observed at doses below 0.75 g/m² and in no case was it unduly distressing.

Five patients (18.5%) developed a widespread eruption which, in the opinion of a dermatologist, was drug-related. In none of these cases was any other medication being taken. All settled with time and in only two cases was antihistamine treatment required for pruritis.

Varying degrees of anorexia, nausea and vomiting were experienced by 17 patients (63%). This occurred at all dose levels but its severity and frequency were greater at doses greater than 1 g/m² and when treatment was continued beyond nine doses. Six patients refused to continue treatment because of anorexia and nausea. All had been prescribed total doses of Ro 03-8799 in excess of 9 g/m².

On two occasions, extravasation of a solution of Ro 03-8799 into the tissues of the antecubital fossa occurred. In neither case were any immediate or delayed local tissue sequelae observed.

Pharmacokinetics

A total of 60 full plasma-time courses were analysed from 31 patients, some of which were reported in preliminary form previously (Roberts et al, 1984). Twenty-four-hour urine was also analysed for 23 patients and 48 h urine for 16 of these. In the large majority of patients the first time course was used in the summary of pharmacokinetic parameters shown in Table II. Pharmacokinetic parameters did not change with multiple dosing. Figure 1A shows a composite plasma-time course for 12 patients following an intravenous infusion of 1 g/m²; two of these were participants in the single dose study, four had single doses of 1 g/m² prior to tumour biopsy and six were part of the multiple dose study. Mean plasma concentrations of the N-oxide metabolite Ro 31-0313 are also shown. Figure 1B shows plasma concentrations of Ro 03-8799 and Ro 31-0313 in a representative individual patient receiving 1 g/m², and Fig. 1C shows data for the only patient receiving the highest dose of 3 g/m².

For the majority of patients, the peak plasma concentration of Ro 03-8799 was seen immediately after the end of the infusion although in some cases the plasma concentration continued to rise, peaking 15 or 30 min later. Plasma concentrations declined biexponentially thereafter, with a rapid distribution phase and a slower elimination phase, and in most cases the data showed a good fit to the two-compartment model. In a minority of patients (Table II) the one-compartment model adequately described the data

TABLE II

SUMMARY OF PHARMACOKINETIC PARAMETERS*

Dose (g/m^2)	n†	Plasma Ro 03-8799 Peak (µg/ml)	$t_{1/2\alpha}$‡ (min)	$t_{1/2\beta}$§ (h)	Vd_{area}¶ (l)	AUC$_{0-\infty}$‖ (µgh/ml)	Clearance (l/h)	Urinary recovery (24 h) Ro 03-8799 (%)	Ro 31-0313 (%)	Plasma Ro 31-0313 peak (µg/ml)
3	1	46.0	15.3	5.68	159	256	19.3	n.d.**	n.d.	6.60
2	2	24.5	—	6.66	187	219	19.4	n.d.	n.d.	7.95
		21.9	53.4	6.08	202	152	23.0	n.d.	n.d.	5.30
1.3	5	25.9±3.3	24.4±18.5 (n = 4)	6.64±1.80	150±27	149±42	16.8±6.9	31.4±5.7	30.2±7.3	7.29±2.28
1.0	12	15.4±3.8	37.0±29.4 (n = 10)	5.87±1.66	178±57	86±25	21.5±6.3	29.3±11.4 (n = 7)	21.0±11.8 (n = 7)	3.84±1.32
0.75	4	10.9±2.0	67.9±37.8	5.61±1.19	162±28	64±12	20.1±2.0	38.8±11.3	34.8±12.8	3.11±0.56
0.5	4	8.9±2.9	42.8±19.7	5.96±1.00	153±51	60±35	18.5±7.2	34.8±16.3	23.5±7.9	3.10±2.14
0.25	3	3.1±0.3	72.7±25.5	7.22±0.27	231±60	20±3	22.1±5.4	23.7±19.1	19.0±7.6	1.17±0.20
Combined***	31	15.8±4.1	44.2±29.9 (n = 27)	6.13±1.39	173±49	95±33	20.2±5.7	31.6±12.2 (n = 23)	25.6±10.8 (n = 23)	4.47±2.01

*Twenty-six out of 31 time courses are for the first dose; in five out of 31 a subsequent dose was used because of missing data or poor curve-fitting. Includes data in preliminary report (Roberts et al, 1984). Results are mean±2 SE

†Total number of patients; where kinetic parameters were calculated from fewer patients than this, n is given for that parameter.

‡Distribution phase half-life, calculated for courses fitting the 2-compartment model

§Elimination phase half-life.

¶Volume of distribution

‖Area under the curve from time 0 to ∞

**n.d. = not determined

***Values of the following dose-dependent parameters are normalised to a dose of 1 g/m^2: peak AUC$_{0-\infty}$, Ro 03-8799 and peak Ro 03-0313.

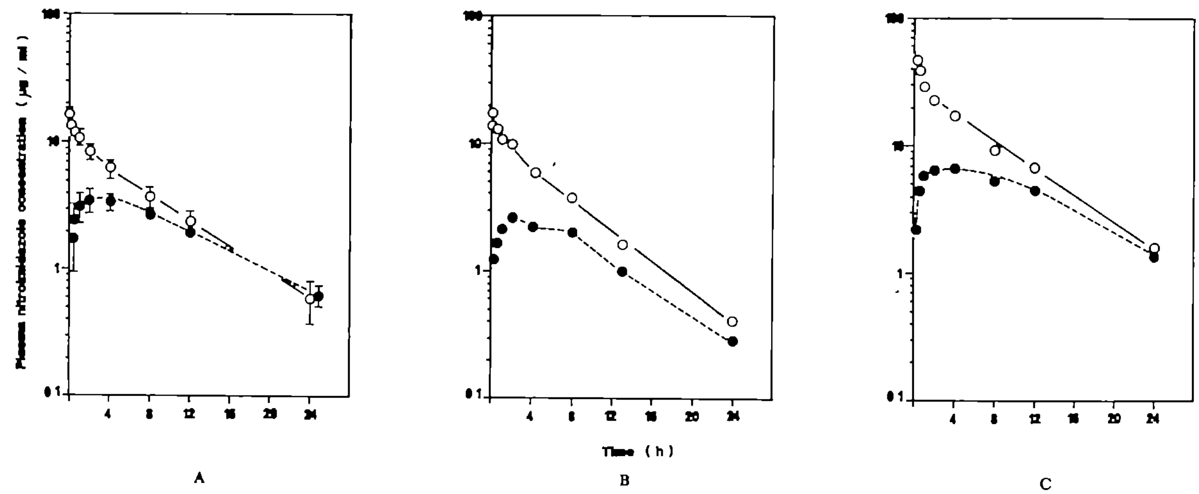

FIG. 1.

Plasma concentrations of Ro 03-8799 (○) and its N-oxide metabolite Ro 31-0313 (●): (A) for all 12 patients (±2 SE) receiving 1 g/m², (B) a representative patient at 1 g/m²; (C) the single patient at 3 g/m²

The following parameters were independent of dose: the distribution half-life ($t_{1/2\alpha}$), the elimination phase half-life ($t_{1/2\beta}$), the volume of distribution (Vd_{area}), the whole body clearance and the urinary recovery of parent compound and metabolite (Table II).

Peak concentration was linearly related to dose (Fig. 2), and the mean peak for all patients normalised to a dose of 1 g/m² was 15.8±4.06 (SD, $n = 31$) The area under the curve ($AUC_{0-\infty}$) likewise showed a linear dependence on dose (Fig. 3) For both parameters the linear fit was excellent, as shown by the small errors (see legends), but the spread of values is clear from the figures. The variation between patients was greater for the peak concentration of N-oxide metabolite Ro 31-0313 (Fig.4), which was normally seen at 1–4 h. The fit to a linear dependence on dose was quite reasonable, but the high-dose data especially were better fitted by a quadratic model. This provides some evidence of saturation kinetics for metabolite production.

The overall mean distribution half-life was 44 min with a large spread (coefficient of variation 68%) while the average elimination half-life was 6.1 h with much less spread (coefficient of variation 22%) (Table II). There was a tendency for the elimination half-life to be slightly longer for males (6.41 ± 1.28 h, SD, $n = 22$) than for females (5.45 ± 1.49 h, SD, $n = 9$) whereas the peak

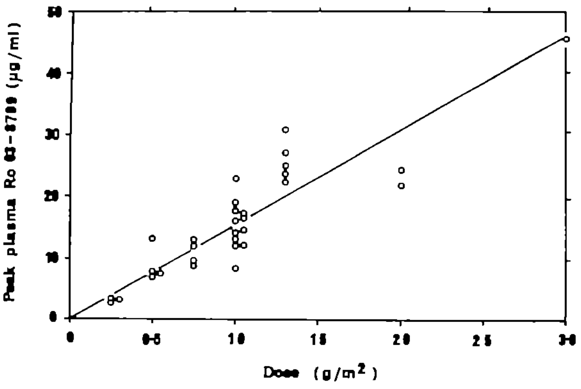

FIG 2.

Relationship between peak plasma Ro 03-8799 concentration and dose. Each Point represents one patient (Table II) The line is the best fit regression for a linear model forced through the origin. The equation is. Peak = 15.56 (±0 66, SE) × dose

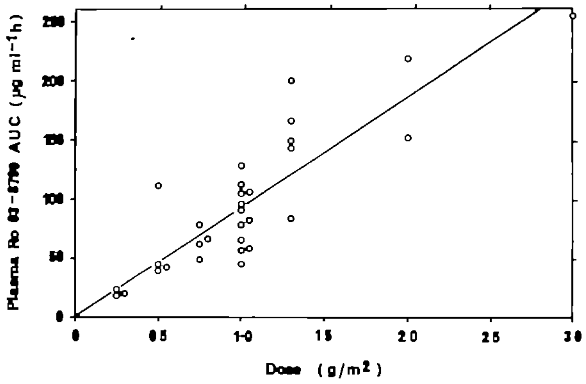

FIG. 3

Relationship between plasma Ro 03-8799 $AUC_{0-\infty}$ and dose Each point represents one patient (Table II) The line is the best fit regression for a linear model forced through the origin. The equation is:

$AUC_{0-\infty}$ = 93 78 (±4 63, SE) × dose

TABLE III

Non-brain tumour tissue concentration of Ro 03-8799 and metabolite Ro 03-0313 after IV injection of 1 g/m²

Case no.	Tumour type	Times of biopsies (h)	Tumour concentration of Ro 03-8799 (μg/g)	Mean tumour/ plasma ratio (%)	Range of ratios (%)	Tumour concentration of Ro 03-0313 (μg/g)	Mean tumour/ plasma ratio (%)	Range of ratios (%)
1	Carcinoma of the breast*	0.25, 2, 4.5	81.6, 45.9, 46.4	651	531–828	1.3, 3.1, 3.3	68	53–80
2	Carcinoma of the breast*	0.5, 1.75, 4	49.6, 16.5, 18.4	433	275–528	1.85, 1.9, 2.7	93	71–113
3	Metastatic squamous carcinoma of the lung*	2, 4	34.4, 23.9	356	364, 349	2.07, 2.83	89	75, 103
4	Carcinoma of the breast*	1, 3, 8, 24.5	65.0, 47.9, 16.4, 2.9	716	541–818	0.63, 4.11, 2.44, 0.44	70	18–97
5	Carcinoma of the buccal mucosa*	1.5	21.9	242	—	2.08	77	—
6	Metastatic carcinoma of the lip*	0.75, 2.25, 7.25	11.6, 13.7, 7.1	135	116–166	2.12, 2.28, 2.49	84	63–114
7	Carcinoma of the breast	0.25	18.2	92	—	BLD†	—	—
8	Basal-cell carcinoma	0.25	97.2	470	—	BLD	—	—
9	Secondary carcinoma of the breast	0.25, 0.5	101.1, 64.2	452	532, 380	2.06, 1.79	86	57–115
10	Carcinoma of the breast	0.083, 0.25, 0.5	66.0, 40.2, 58.0	277	155–355	0.38, 0.54, 1.54	73	22–142
11	Carcinoma of the breast	0.083	21.8	87	—	BLD	—	—

*Published previously in preliminary form (Roberts et al, 1984).

†BLD = below limit of detection.

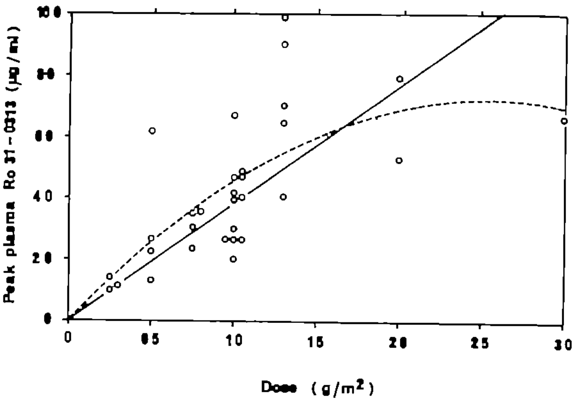

FIG. 4

Relationship between plasma Ro 0313 metabolite concentration and dose. Each point represents one patient (Table II). The solid line is the best fit regression for a linear model forced through the origin, for which the equation is:

Peak metabolite = 3.83 (±0.31, SE) × dose

The dashed line is the best fit regression for a quadratic model forced through the origin, for which the equation is

Peak metabolite = [5.76 (±0.61, SE) × dose] − [1.11 (±0.33, SE) × dose^2]

concentrations were identical at 15.8±4.2 µg/ml and 15.5±3.8 µg/ml, respectively.

About 32% of the dose was recovered unchanged in the urine at 24 h, with a further 26% as the N-oxide and 42% unaccounted for (Table II). In the second 24 h collection period only a further 3% Ro 03-8799 and a further 5% of the metabolite were recovered. The average whole body clearance of Ro 03-8799 was 20.1 l/h which gives an estimate of 6.8 l/h for renal clearance.

Tumour Table III shows tumour concentrations and tumour/plasma ratios of Ro 03-8799 and the metabolite Ro 31-0313 for 11 accessible tumours at various times after intravenous administration of 1 g/m^2. Table IV shows tissue concentrations and tissue/plasma ratios for brain tumour and macroscopically normal brain tissue in a further nine patients at various times after administration of the same dose. In every case where multiple biopsies were obtained, the highest absolute Ro 03-8799 concentration was seen at the earliest time point. In the two patients biopsied at 5 min after injection the concentrations were 66.0 µg/g and 21.8 µg/g, respectively. Mean concentrations at 15 min and 30 min were, respectively, 65.3±27.2 (2 SE, $n = 6$) µg/g and 57.3±8.4 (2 SE, $n = 3$) µg/g, giving an overall mean of 62.6±17.9 (2 SE, $n = 9$) µg/g. Tumour concentrations then fell in parallel with the plasma.

In 17 out of 20 patients the mean tumour/plasma ratio exceeded 100%, and in only three patients (Cases 7, 11 and 16) did at least some of the tumour tissue fail to accumulate the drug to a higher level than in the corresponding plasma. We have not assessed micro-

TABLE IV

BRAIN AND BRAIN TUMOUR CONCENTRATIONS OF Ro 03-8799 AND METABOLITE Ro 31-0313 AT VARIOUS TIMES AFTER IV ADMINISTRATION OF 1 g/m^2

Case no	Tumour type	Time of biopsy (h)	Tissue concentration of Ro 03-8799 (µg/g)		Tissue/plasma ratios (%)		Tissue concentration of Ro 31-0313 (µg/g)		Tissue/plasma ratios (%)	
			Viable (necrotic) tumour	Normal brain	Viable (necrotic) tumour	Normal brain	Viable (necrotic) tumour	Normal brain	Viable (necrotic) tumour	Normal brain
12	Astrocytoma	1.75	7.68 (68)	26.1	82 (721)	277	1.13 (5.05)	0.531	16 (69)	7
13	Astrocytoma	6.75	17.8 (8.39)	18.6	546 (257)	571	4.16 (2.74)	0.724	81 (54)	14
14	Astrocytoma	2.25	14.5	30.2	266	554	0.632	0.521	18	15
15	Astrocytoma*	0.25	53.6 (48.6)	47.4	450 (408)	398	BLD†	BLD	—	—
16	Astrocytoma	0.75	1.50 (3.98)	19.2	18.2 (48.5)	23.4	BLD	BLD	—	—
17	Astrocytoma	5.75	12.5	9.99	379	303	BLD	0.407	—	23
18	Astrocytoma*	1.25–2	23.0 (11.7)	30.8	289 (182)	413	0.584 (0.823)	BLD	30	—
19	Astrocytoma	3.0	17.9	18.9	411	434	0.636	BLD	17	—
20	Secondary cylindroma	12.5	8.26	5.88	365	452	1.93	BLD	102	—

*Published previously in preliminary form (Roberts et al, 1984)
†BLD = below limit of detection

scopically the amount of viable versus non-viable tissue in our samples. Macroscopically, the samples from patients 5, 6 and 7 appeared to contain appreciable portions of necrotic material, and in these cases the tumour/plasma ratios were relatively low. In Case 2, however, a low tumour concentration of drug was found in that portion of the tumour judged by the neurosurgeon to be viable. It is of interest that in this case, and one other (Case 14) there was a higher concentration of drug in tissue judged by the neurosurgeon to be necrotic tumour.

Brain tumour tissue appeared to concentrate Ro 03-8799 to a similar extent to other tumour types, the mean of average tumour/plasma ratios for each patient being 329±88% (2 SE, $n = 9$) for the brain tumours compared to 355±129% (2 SE, $n = 11$) for the others. The overall mean for the 20 patients was 336±86%. In eight out of nine cases where samples of macroscopically normal brain were also removed at the time of neurosurgery for brain tumours, Ro 03-8799 was found to be higher than in the corresponding plasma. The patient with low normal brain levels (Case 16) also had low tumour levels. The mean normal brain concentration of 381±111% (2 SE, $n = 9$) was almost identical to that for the corresponding tumours.

In contrast to a previous report (Allen et al, 1984) we were able to identify the N-oxide metabolite in tissue, including brain. In eight of 11 non-brain tumours where it was detectable, the mean tissue/plasma ratio was 80%, in six out of nine brain tumours it was 46% and in four of nine normal brains it was 15% Thus, unlike the parent compound, the metabolite does not accumulate in tissue, and there is evidence of exclusion from the brain.

DISCUSSION

We have established that an acute central neurotoxicity is dose-limiting for the novel basic radiation sensitiser Ro 03-8799. The toxicity syndrome consists of a variable combination of: a subjective feeling of heat, flushing, chemical taste, nausea, vomiting, anorexia and disorientation at doses which might be used repeatedly in combination with radiation At the highest single dose given (3 g/m^2) a severe and distressing acute toxicity syndrome was observed which culminated in a coma of 1 75 h duration. Other minor toxicities, such as short-lived peripheral paraesthesiae and a drug-related rash, were observed. No long-term sequelae have been observed In particular there have been no instances of peripheral neuropathy.

The mechanism of the acute central neurotoxicity is unknown, although it has been postulated that the drug has a neuroleptic action (Dische, personal communication) High concentrations of the drug had been found in brain tissue in mice (Williams et al, 1982b) and we have found that it is similarly concentrated in macroscopically normal human brain (see below). In one patient with particularly severe central nervous symptoms an electro-encephalogram was performed Recording was started 15 min before infusion of the drug and continued during the infusion and for 15 min after its completion. No electro-encephalographic abnormality was observed at any time during the recording.

Many radiotherapy departments, including our own, commonly employ a 3 fractions-per-week radiation regime, and for this reason we investigated the toxicity of the drug when administered thrice weekly. The acute central neurotoxicity did not allow escalation of total dose beyond 12 g/m^2 given in doses of 1 g/m^2 over a total of four weeks. Even at this dose level, two out of five patients refused further doses of the drug after four and six doses, respectively.

In general the pharmacokinetic parameters for plasma and urine were very similar to those obtained previously by ourselves (Roberts et al, 1984) and others (Saunders et al, 1982, 1984; Allen et al, 1984). For example, our mean elimination half-life for the 31 patients in our study was 6.1 h compared with 5 1 h for the 69 patients studied by Saunders et al (1984). We confirm in a larger series the rapid whole body clearance (20.1 l/h) and renal clearance (6.8 l/h) noted by Allen et al (1984) (20.0 l/h and 5.4 l/h, respectively) and likewise confirm the high volume of distribution, indicative of good tissue penetration (173 l compared with 155 l). We have, however, obtained a larger estimate for the distribution half-life (44 min) than did Allen et al (1984) in their small series (10 min) but the variation in this parameter is very large in both studies. In addition, Allen et al (1984) found that plasma levels of the N-oxide metabolite were not dose-related at doses greater than 0.2 g whereas, although we did find some evidence for saturation of this metabolic pathway, this was only really significant at doses above 1 g/m^2. We have also found rather higher urinary recoveries of Ro 03-8799 (34%) and Ro 31-0313 (31%) than did Allen et al (1984) (16% and 12%, respectively).

Earlier low-dose studies had shown concentration of Ro 03-8799 within tumour tissue, as compared with corresponding plasma levels, by a factor of 3 or more (Saunders et al, 1982). We have confirmed this at higher doses of the drug, of the order which might be used therapeutically Our overall mean tumour/plasma ratio of 336% is essentially identical to that of 340% obtained by Saunders et al (1984). A similar three-fold concentration is seen with cells held at neutral extracellular pH *in vitro* (Dennis et al, 1985), the effect being due to the slightly lower intracellular pH causing an accumulation of the basic drug by ion trapping The concentration of Ro 03-8799 over plasma is not unique to tumour tissue We have demonstrated an average 3.8-fold concentration in macroscopically normal brain and tissue/plasma concentrations up to seven times have been reported for other normal human tissues (Saunders et al, 1984).

It is critical to compare tumour concentrations of Ro 03-8799 and MISO which might be achieved by reasonable therapeutic doses. Although Ro 03-8799 is given intravenously, peak plasma concentrations per unit of dose administered are lower than with MISO. This is because Ro 03-8799 has a larger apparent volume of distribution. Thus peak plasma concentrations of MISO are approximately 25 μg/ml per gramme administered, (or roughly 43 μg/ml per g/m^2) whereas in the present study the equivalent figure for Ro 03-8799 is 8.9 μg/ml per gramme (or 15.7 μg/ml per g/m^2) Saunders et al (1984) reported a similar figure of 14.8 μg/ml per g/m^2 for doses up to 0.75 g/m^2 In addition, because Ro 03-8799 has a higher molecular weight (254) than MISO (201), the plasma concentrations in molar terms are 0.035 mM and 0.124 mM per administered gramme and 0.061 mM and 0.214 mM per administered g/m^2 for Ro 03-8799 and MISO respectively.

This difference is more than compensated for, however, by the accumulation of Ro 03-8799 in tissue. This accumulation might appear to offer a marked advantage over MISO which, in common with other neutral nitroimidazoles, gives tumour concentrations which are typically 70–80% of the plasma concentration at the corresponding time (Workman, 1983). In the present study, peak tumour Ro 03-8799 concentrations were invariably seen at the earliest time points (5 min, 15 min and 30 min). A previous study found levels 51% higher at 15–18 min than at 29–30 min (Saunders et al, 1984). Since there was no advantage for prolonged contact with the drug in mouse tumours (Williams et al, 1982b) it was advised that radiotherapy be given at 20 min rather than 30 min. With doses of 1 g/m^2 we have obtained mean tumour Ro 03-8799 concentrations of 65.3 μg/g or 0.257 mM at 15 min ($n = 6$) and 57.3 μg/g or 0.225 mM at 30 min ($n = 3$), also suggestive of a slight advantage for the earlier time. Our very limited data at 5 min show that concentrations might be even higher at this time. The overall mean for our 15 min and 30 min data is 62.6 μg/g or 0.247 mM ($n = 9$). On the basis of a 75% tumour/plasma ratio, the equivalent peak value for the same dose of MISO would be 32.3 μg/g or 0.160 mM. The achieved tumour concentration of Ro 03-8799 is, therefore, 1.5 times that of MISO for the same administered dose.

We can now consider what sensitiser enhancement ratios would be predicted from these achieved doses by inspecting concentration–effect data obtained *in vitro* and *in vivo*. The data for hypoxic V79 cells *in vitro* (Smithen et al, 1980; Watts, unpublished) summarised by Williams et al (1982a) demonstrates that Ro 03-8799 is up to 10 times more efficient than MISO on the basis of *medium* concentrations required for a given level of sensitisation. Taking into account the *in vitro* intracellular/extracellular drug concentration ratios of 0.7 for MISO and 3.3 for Ro 03-8799 at neutral extracellular pH (Dennis et al, 1985), the latter can be seen to be 2.1 times as efficient on the basis of *intracellular* concentrations required for a given level of sensitisation An intracellular concentration of 0.25 mM Ro 03-8799 gives a sensitiser enhancement ratio of 1.6 compared with 1.3 for 0.16 mM MISO. A concentration of 0.84 mM MISO would be required to give the same sensitisation as 0.25 mM Ro 03-8799; *i.e.* 3.4 times as much MISO would be required.

Considering now the only available *in vivo* data, using the fibrosarcoma SA FAb in mice, Williams et al (1982a) showed that on the basis of measured tumour concentrations Ro 03-8799 was up to four times more potent than MISO at high concentrations, but there was no significant difference below about 0.12 mM. At 0.25 mM the enhancement ratio for Ro 03-8799 is 1.5 compared to 1.25 for 0.16 mM MISO. The concentration of MISO required to be equiactive with 0.25 mM Ro 03-8799 is 0.45 mM; *i.e.* 1.8 times as much MISO would be required.

The disparity between the predictions based on *in vitro* versus *in vivo* data may be related to differences in intracellular drug concentrations and/or pH in these two situations or, more likely, to the lower precision of the *in vivo* assay (Wardman, personal communication) Further comparisons with other lines, both *in vitro* and *in vivo*, would be desirable. On the basis of the data available at the moment, Ro 03-8799 is likely to be between 1.8 and 3.3 times as effective as MISO. Since the precision of the *in vitro* assay is greater, the latter estimate is likely to be the most accurate An additional factor to be considered is that Ro 03-8799 is concentrated in areas of viable tumour (Saunders et al, 1984), in which case one would expect local concentrations of drug which exceed those measured in whole tumour. Furthermore, studies with radiolabelled Ro 03-8799 have shown that levels of radioactivity were consistently twice those of Ro 03-8799 itself, measured by HPLC (Saunders et al, 1982, Allen et al, 1984). Metabolism may occur *ex vivo* despite rigorous handling procedures, and concentrations of intact drug may be up to twice those measured.

The incidence of acute central nervous system toxicity at doses greater than 1 g/m^2 suggests that peak plasma concentrations should not exceed an average of approximately 15 μg/ml, which corresponds to a concentration of about 57 μg/g in brain tissue. We are currently analysing our data to see if toxicity can be predicted from plasma pharmacokinetics on an individual patient basis.

It has proved possible (Saunders et al, 1984) to administer Ro 03-8799 in daily doses of 0.75 g/m^2 to a total dose of 22.5 g/m^2 over 6 weeks. Although one would expect peak tumour concentrations to be fractionally lower than those we have found at 1 g/m^2 (*i.e.* of the order of 0.22 μmol/g), it may be that the combination of greater potency, higher total dose, and concentration of Ro 03-8799 in tumour will enable a benefit over MISO to be demonstrated clinically.

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Antibody-guided radiolocalisation of tumours in patients with testicular or ovarian cancer using two radioiodinated monoclonal antibodies to placental alkaline phosphatase

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ABSTRACT

Monoclonal antibodies (H317 and H17E2) against placental-type alkaline phosphatase and testicular placental-like alkaline phosphatase were radiolabelled with ^{123}I or ^{131}I and used in a prospective study of patients with germ-cell neoplasms of the testis (13 studies) or epithelial-origin neoplasms of the ovary (13 studies). The presence of tumour was confirmed in the majority of patients with active disease by antibody scanning. The absence of tumour was confirmed in all cases in patients in complete remission. In two patients with positive antibody scans but no disease found by conventional radiological evaluation, further investigations subsequently revealed the presence of tumour.

A positive antibody scan indicates the definite presence of a tumour, although a negative antibody scan does not always exclude the presence of disease. This method may be of clinical value in establishing disease status in patients with potentially curable diseases such as ovarian or testicular cancers

Monoclonal antibody-guided radiolocalisation of cancer promises to be of value in improving the diagnosis of at least some forms of malignant disease. Radiolabelled tumour-associated monoclonal antibodies have already been shown to be capable of localising preferentially to neoplastic tissues (Mach et al, 1981; Farrands et al, 1982; Epenetos et al, 1982, Rainsbury et al, 1983; Epenetos, 1983a). However, careful evaluation of the biodistribution of radiolabelled antibodies can show that some antibodies also localise to normal epithelial as well as lymphoid tissues (Epenetos, 1983a). This can reasonably be predicted by prior study of monoclonal antibody reactivity on tissue sections of both normal and neoplastic tissues. Using immunohistochemical methods (Arklie et al, 1981), positive tissue reactivity indicates a potentially positive antibody scan when the same antibody is used *in vivo*. Thus, in the search for "better" radioimmunolocalising antibodies, a restricted specificity is required, *i.e* antibodies with no, or low, reactivity with normal tissues but high reactivity with neoplastic tissues.

Placental alkaline phosphatase (PLAP) has been shown to be expressed on the surface membrane of many epithelial ovarian cancers and testicular germ-cell tumours (Epenetos et al, 1984; Doellgast & Homesley, 1984). Serum PLAP has also been assayed in patients with testicular germ-cell tumours and only patients with active seminomatous tumours were found to have consistently elevated serum PLAP (Epenetos et al, 1985). Using immunohistological methods on fresh frozen tissues we found no staining reactions for PLAP on cells of any normal tissues (except term placenta) (Epenetos et al, 1984); the antigen, however, is expressed at trace levels in some normal tissues (McLaughlin et al, 1984a). In experimental models both polyclonal and monoclonal antibodies against PLAP produced good immunolocalisation of PLAP-producing tumours (Epenetos, 1983b; Jeppsonn et al, 1984).

PATIENTS AND METHODS

Twelve patients with ovarian cancer, aged 30–75 (mean 55) years were studied (13 studies), as well as 12 male patients with germ-cell tumours of testis aged 20–35 (mean 22) years (13 studies). All patients gave their written informed consent prior to entering the study. They were skin tested for hypersensitivity to mouse immunoglobulin and received potassium iodide 120 mg/day for 7 days starting one day before the procedure (Epenetos et al, 1982).

Monoclonal antibodies

H17E2. This mouse IgG$_1$ was raised against purified plasma membranes of normal term placenta. It precipitates placental alkaline phosphatase activity at a single band of 67000 daltons consistent with the molecular weight of PLAP (Travers & Bodmer, 1984) It also reacts with the leucine-inhibitable form of alkaline phosphatase found at low levels in the normal testis and which is cross reactive with the placental enzyme (Harris, 1982). It does not react with other non-placental forms of alkaline phosphatase.

H317. This mouse IgG$_1$ was produced by immunising with syncytiotrophoblast microvilli preparations from

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Workers involved in this study include: A. A Epenetos, Group Co-ordinator, W F Bodmer, A Branson, D. Carr, A Constable, N Courtenay-Luck, H. Durbin, S. Field, H Gregory, K E. Halnan, B. Henderson, G Hooker, P. M Johnson, J. Lambert, J. P Lavender, W. G MacGregor, C. G McKenzie, P. J McLaughlin, A. J. Munro, R. D T. Oliver, T. Pawlikowska, J S Orr, D. Snook, S Stewart, P Travers.

term placentae. It has been shown to be specific for the heat-stable L-phenylalanine-inhibitable PLAP. It is unreactive with the testicular variant of PLAP and other non-placental forms of alkaline phosphatase (McLaughlin et al, 1982, 1984b).

Antibodies were produced in batches by culturing the hybridomas in tissue culture medium (RPMI/1640). The average concentration of immunoglobulin was 10 μg/ml. Pure immunoglobulin was obtained by passing supernatants through a sterile protein-A-"Sepharose" column and eluting with 0.1 M citrate buffer of decreasing pH (Ey et al, 1978). Purity was confirmed by isoelectric focusing (Awdeh et al, 1968) and by polyacrylamide-gel electrophoresis (Laemlli, 1970). The pH of the eluate was adjusted with "Tris" (hydroxymethyl-amino-methane) to pH 7.0 and the antibody concentration adjusted to 1 mg/ml The final solution was "millipore"-filtered into sterile ampoules in 2 ml aliquots. Ten per cent of the ampoules were tested for sterility and apyrogenicity by an independent laboratory (Safepharm Labs). Ampoules were stored at 5°C for up to 6 months with no detectable loss of antibody reactivity as tested in binding assays.

Iodination. Antibodies were iodinated with ^{123}I (AERE Harwell) or ^{131}I (Amersham International IMS 30.1) using the iodogen method (Fraker & Speck, 1978). Free iodine was removed by gel filtration using Sephadex G50 in a sterile 20 ml syringe and eluted with phosphate-buffered saline (PBS) pH 7.4. The Sephadex G50 was prewashed with 1% human serum albumin (HSA).

Radiolabelled antibodies were diluted in 1% HSA (final volume 5–10 ml) and "millipore"-filtered prior to patient administration.

Reactivity of antibodies

Before and after iodination, antibody reactivity was tested in an enzyme-linked immunosorbent assay (ELISA) (Lansdorp et al, 1980) and in a direct radioimmunoassay (RIA) including a competitive assay with unlabelled antibodies. Purified placental membranes were used as targets for the antibodies in the immunoassays. Samples of radiolabelled antibodies were gel-filtered through a Sephadex G150 column (55 cm × 2 cm) to detect antibody aggregates

Radioactivity counting in tissue and autoradiographs

The selective localisation of injected, iodinated, monoclonal antibodies in tumours compared with other normal organs was demonstrated in some patients with ovarian cancer by counting the radioactivity in representative weighed samples of resected tissues and by autoradiography (ARG). Autoradiographs were prepared using Ilford K5 fluid emulsion Tissue sections were exposed for 7–30 days at 4°C. Sections were then developed, fixed and stained with haematoxylin for light microscopy. Four patients having ARG were injected with a small amount (50–100 μCi) of ^{125}I-labelled anti-PLAP antibody, concurrently with ^{123}I-labelled antibody.

Quality control

All reagents used in the radiolabelling procedures were prepared and assessed to be sterile by Miss B. Street, Senior Pharmacist, Hammersmith Hospital.

Measurement of specificity and sensitivity

Specificity and sensitivity are statistical indices of the efficiency of a diagnostic test (Yerushalmy, 1947). Specificity indicates the capacity for correct diagnosis in confirmed negative cases for the disease, while sensitivity indicates the capacity for correct diagnosis in confirmed positive cases. Furthermore, for a test to be clinically useful it is important to know its predictive value with regard to the accuracy of positive and negative diagnoses.

Criteria for positive (abnormal), equivocal, and negative (normal) findings

These were based on the consensus of opinions of three observers (A A.E., J P.L., D.C.) who examined antibody-guided scans without employing any subtraction methods.

(a) *Normal findings* these indicate the distribution of radioactivity in the blood pool (heart, major vessels, liver) clearly seen in early scans (up to 1 h after injection) and only changing in degree of distribution with later scans (24 h, 48 h or later after injection).

(b) *Abnormal findings*·

(i) focal abnormalities were noted as clearly defined "hot spots",

(ii) diffuse abnormalities were noted as obvious differences in the intensity of radioactivity between a body region and background, this difference not being seen in the early blood-pool scans.

(c) *Equivocal findings* were those thought not to be negative, but also not convincingly positive, as judged by the three observers. This category was found to be the most difficult to score

RESULTS

Monoclonal antibodies H17E2 and H317 were radiolabelled to a specific activity of 4–8 mCi/mg. Free radioiodine was removed on 20 ml Sephadex G50 in a sterile syringe and the final solution contained less than 0.5% free radioiodine There was no loss of antibody immunoreactivity as tested in binding assays and there was no immunoglobulin-aggregate formation during or after the iodination procedures.

Tables IA and IB summarise the histological diagnoses of the patients and the administered antibodies and compare the findings of conventional investigations (including X-ray, CT scanning, and ultrasound examinations, laparoscopy and peritoneal washings, and laparotomy) with those of antibody-guided scanning Figure 1 shows the amount of radioactivity (cpm/g) in resected samples of tumour and

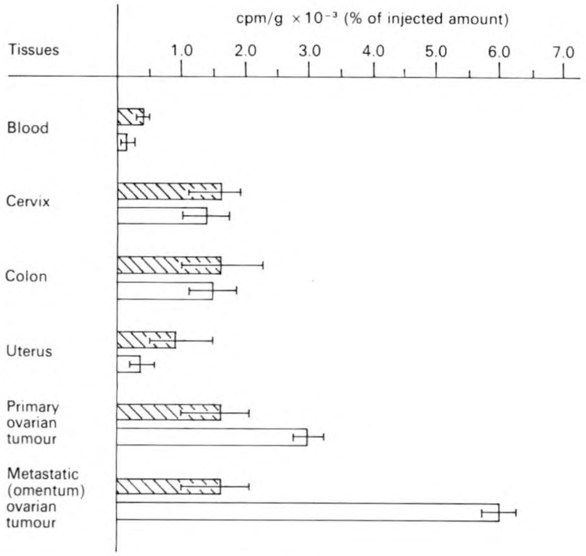


FIG. 1.

Distribution of radioactivity in tissues 5 days after injection of ^{125}I-labelled H317 antibody in two patients with ovarian cancer (▧ and □). In one patient (▧) there is no difference in antibody uptake between tumour and normal tissues while in the other patient (□) there is significantly higher antibody uptake by tumour (particularly metastatic) than normal tissues. The horizontal solid lines show standard deviation obtained with different samples from the same specimen.

normal tissues in two patients with ovarian cancer. As can be seen, in one patient there was no preferential tumour uptake of antibody, whilst in the other patient a significant difference in antibody uptake can be seen between normal and neoplastic tissues. Figure 2A shows the antibody-guided scan (AG scan) of a patient with primary ovarian cystadenocarcinoma. Figure 2A was taken 5 min after injection of ^{123}I-H317 and outlines the blood-pool image. Figure 2B was taken 45 h after injection of antibody. It demonstrates marked uptake on the left side and some uptake on the right side of the pelvis. Figure 2C is a tomographic section taken at 45 h, *i.e.* at the same time as Fig. 2B. This demonstrates clearly that the uptake in the left side of the pelvis, corresponding to tumour, is quite separate from uptake due to free ^{123}I in the bladder. Also, there is uptake on the right side of pelvis. Following these scans the patient underwent laparotomy, and a large cystadenocarcinoma (5 cm diameter) of the left ovary was found and removed. The anatomical location of the tumour corresponded well with the findings of antibody-guided scanning. Figure 3A shows the antibody scan of a patient with a pleural metastasis from seminoma of testis. The scan was taken 48 h after injection of ^{123}I-H17E2. This demonstrates clearly the metastatic lesion at the right, lower pleural space, as confirmed by CT scanning of the chest (Fig. 3B). Figure 3C was taken at 48 h using H17E2 labelled with ^{131}I. This failed to

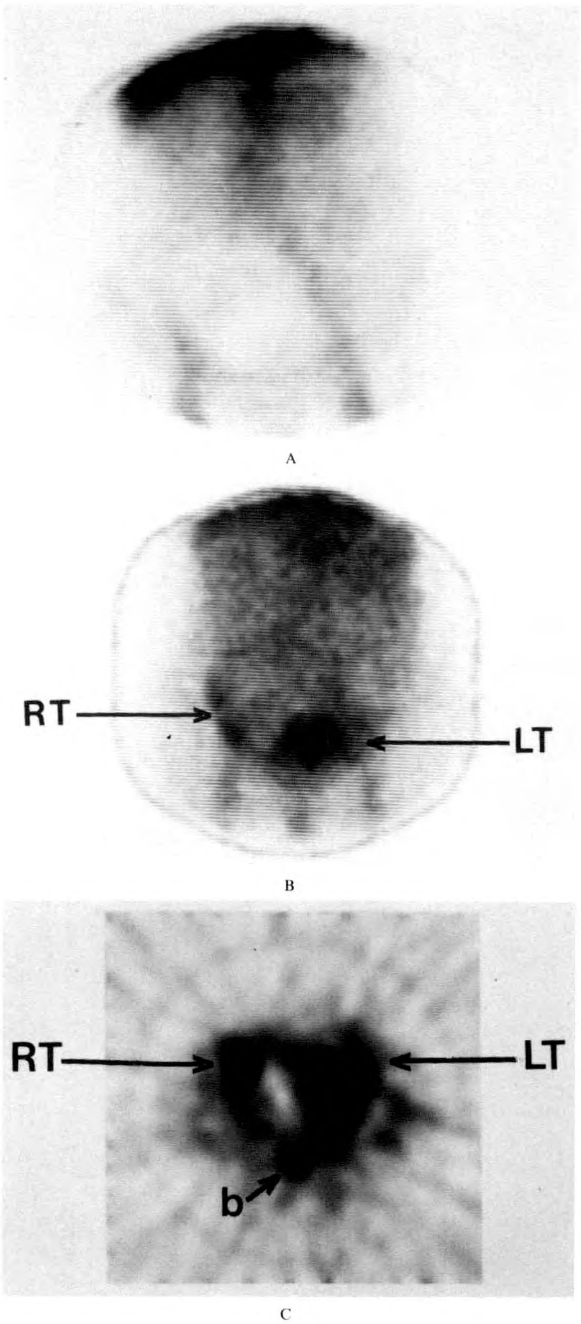


FIG. 2.

(A) Radionuclide scan 5 min after injection of ^{123}I-H317 in a patient with ovarian cancer in the pelvis. The blood-pool image is outlined. (B) Scan 45 h after injection of ^{123}I-H317 in the same patient as in (A) showing uptake in the left (LT) and right (RT) side of pelvis attributable to a tumour mass. (C) A tomographic section taken at the same time as (B) illustrating that the uptake in the left pelvic tumour mass (LT) is quite separate from uptake due to free ^{123}I in the bladder (b). Also note uptake in the right pelvic tumour mass (RT).

TABLE IA

PATIENTS WITH OVARIAN CANCER

Case	Age (years)	Histology	Labelled antibody	Findings of antibody-guided (AG) scan	CT scan	Surgical and other findings	Comment	Correlation of findings
1	70	Adenocarcinoma	^{123}I-H317	Equivocal uptake at left iliac region 24 h after injection	Negative	Positive washings at laparoscopy		+
2	40	Cystadenocarcinoma	^{123}I-H17E2	Focal uptake in left pelvis extending to right side of abdomen 24 h after injection		Large (5 cm diameter) left ovarian cystadenocarcinoma	See Fig. 2.	+
3	41	Cystadenocarcinoma	^{123}I-H17E2	(a) Focal uptake left lower abdomen 24 h after injection	(a) Ascites	(a) Ascites		+
				(b) Diffuse uptake in abdomen 24 h after injection	(b) Possible mass in left pelvis	(b) Palpable mass in pelvis		
				(c) No uptake in liver	(c) Doubtful mass in liver			
4	75	Adenocarcinoma	^{123}I-H317	Focal uptake left side of pelvis 24 h after injection	Mass at left sacroiliac joint region			+
5	70	Cystadenocarcinoma	^{123}I-H17E2	Equivocal uptake in mid-line of lower pelvis at 24 h after injection		Tumour involving left ovary, uterus, omentum and right external lymph nodes		+
6	65	Papillary	^{131}I-H17E2	Negative	Hepatic metastasis (1–2 cm diameter) in right lobe posteriorly			–
7	68	Cystadenocarcinoma	^{131}I-H17E2	Negative	Negative	Residual disease (< 1 cm diameter)		–

8	50	Papillary	^{123}I-H17E2	Equivocal uptake at left sacroiliac area	Negative	Positive washings at laparoscopy	+
9	50	Adenocarcinoma	^{123}I-H17E2	Negative	Negative	Residual disease (< 1 cm diameter) at second-look laparotomy after chemotherapy	−
10	70	Cystadenocarcinoma	^{123}I-H17E2	(a) Diffuse uptake in abdomen at 24 h (b) Focal artefact at site of biopsy of right inguinal region 1 day prior to AG scan	Mass in pelvis		+
11	50	Papillary	^{123}I-H317	Equivocal focal uptake at right hypochondrium at 24 h	Negative	Residual disease (< 1 cm diameter) at second-look laparotomy after chemotherapy	+
12	60	Papillary	^{131}I-H17E2	(a) Focal uptake in pelvis at 48 h (b) Focal uptake in left lower abdomen at 68 h	Negative	Residual disease (< 1 cm diameter) at second-look laparotomy after chemotherapy	+
13	75	Papillary	^{131}I-H317	(a) Diffuse uptake in abdomen at 24 h (b) Focal uptake in central pelvis (c) Focal uptake in right hypochondrium	Ascites but no masses were seen clearly	Palpable mass in pelvis	+

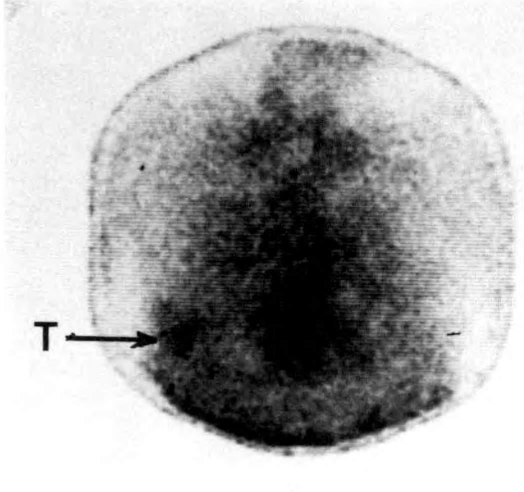
TABLE IB

PATIENTS WITH TESTICULAR CANCER

Case	Age (years)	Histology	Labelled antibody	Findings of antibody-guided scan	CT scan	Surgical and other findings	Comment	Correlation of findings
14	32	MTT	^{123}I-H17E2	Negative	Negative		Patient in complete remission at time of scan	+
15	35	Seminoma	^{123}I-H17E2	(a) Equivocal uptake in left hypochondrium at 24 h (b) Equivocal uptake in left iliac nodes at 24 h	Abnormal lymphadenopathy in left iliac and para-aortic regions			+
16	25	MTU	^{123}I-H17E2	Negative	Mass (1 cm) in right lung	Mass excised non-viable necrotic tissue		–
17	30	MTU	^{123}I-H17E2	Focal uptake in left chest at 24 h	Tumour seen on chest radiograph including left lung			+
18	23	MTT + choriocarcinoma	^{123}I-H17E2	Negative	Mass (1 cm) in right lung	Positive cytology	Patient had allergic reaction to antibody; injection thus technically unsatisfactory	–
19	25	MTU	^{123}I-H17E2	(a) Negative (b) Uptake in spleen due to aggregate formation	Left para-aortic adenopathy and liver metastases seen on CT scan taken 1 month after AG scan			–
20	30	Seminoma	^{123}I-H17E2	Equivocal focal uptake in upper border of right side of liver	Possible small (1 cm) liver metastasis right side			+

21	30	Seminoma	^{123}I-H17E2	Equivocal uptake in pelvic bones and skull	Bone marrow infiltration with seminoma			+
22	25	MTT	^{123}I-H17E2	Negative	Negative		Patient in complete remission	+
23	35	Seminoma	^{123}I-H17E2	(a) Focal uptake right side lower chest at 24 h more obvious at 48 h (b) Equivocal uptake at midline of pelvis at 24 h	Pleural lesion right side of chest	Seminoma cells aspirated right pleural lesion		+
24	35	Seminoma	^{131}I-H17E2	Negative	Pleural lesion right side of chest		Poor imaging with ^{131}I	–
25	30	MT-mixed	^{123}I-H17E2	Negative	Negative		Patient in complete remission	+
26	28	Differentiated teratoma previous MTT	^{123}I-H17E2	(a) Negative abdomen (b) Focal uptake right iliac region	(a) Large abdominal mass (b) Right iliac region normal on CT		(a) Differentiated teratomas are negative for PLAP (b) Right iliac region may either represent uptake in MTT residual tumour or may represent false positive localisation	+

MTT, malignant teratoma, trophoblastic; MTU, malignant teratoma, undifferentiated; MT—mixed, malignant teratoma and seminoma + indicates good correlation between antibody scanning and other findings; – indicates poor corrlation between antibody scanning and other findings.



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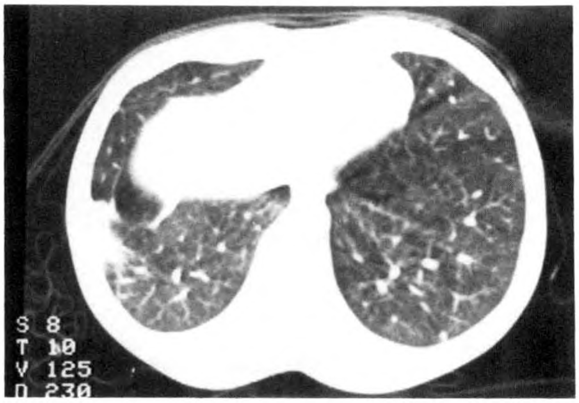

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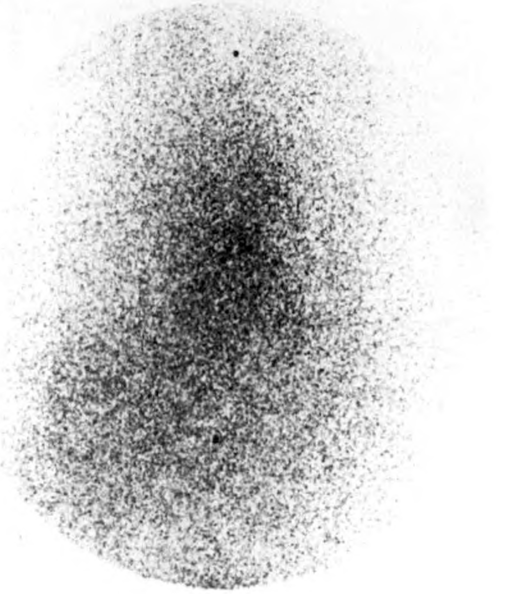

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FIG. 3.

(A) Radionuclide scan 46 h after injection of ^{123}I-H17E2 in a patient with a right pleural metastasis secondary to seminoma of testis. Note tumour lesion (T) at right lower pleural area. (B) CT scan of the same patient as in (A) showing the site of the pleural lesion secondary to seminoma. (C) Radionuclide scan 48 h after injection of ^{131}I-H17E2 in the same patient as in (A). The tumour site is not shown, in contrast to Fig. 3A where the same antibody was labelled with ^{123}I.

demonstrate the tumour site, in contradistinction to Fig. 3A. An autoradiograph of a tissue section of ovarian adenocarcinoma, resected 48 h after injection of H317 labelled with ^{125}I, showed the distribution of radiolabelled antibody on the surface of ovarian carcinoma cells as well as in the lumen of adenocarcinoma tissue.

With regard to ovarian cancer, the sensitivity in this antibody-guided scanning test was 10/13 (77%), and with regard to testicular germ-cell cancer, the sensitivity of the test was 6/10 (60%) with a specificity of 3/3 (100%).

DISCUSSION

This study has shown that radiolabelled antibodies to PLAP can produce successful imaging of tumour masses by external body scintigraphy in patients with ovarian and testicular cancer. The images obtained compared favourably with those previously obtained using antibodies such as HMFG2 (Epenetos et al, 1982), in that smaller masses were visualised in more central parts of the body (Fig. 2A).

The quality of images was better when ^{123}I was used rather than ^{131}I (compare Fig. 3A with Fig. 3C). Thus, it is recommended that ^{123}I is used in tumour radioimmunolocalisation studies. Dehalogenation of ^{123}I is a problem which can cause uptake of free ^{123}I by normal thyroid, stomach and other organs. The quality of the images may be improved by the use of alternative labels such as ^{111}In (Hnatowich et al, 1983), although ^{111}In-labelled antibodies give intense liver images, precluding their use for imaging liver metastases (Rainsbury et al, 1983). It may thus be desirable to use ^{123}I-labelled antibody for imaging the liver area, followed by ^{111}In-labelled antibody for the rest of the body.

Not all patients with ovarian or testicular cancer had positive antibody scans in this study; this may be due to variable expression of PLAP in tumours among different patients and different tumour sites. In this respect, immunoassays for serum PLAP that have been described recently (McLaughlin et al, 1983; Epenetos et al, 1985) may be helpful in selecting patients with high serum and, thus, high tumour-PLAP content.

In summary, monoclonal antibodies H17E2 and H317 to different determinants of placental-type alkaline phosphatase and testicular PLAP-like alkaline phosphatase perform well as radioimmunolocalising agents in patients with ovarian and testicular cancer.

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Book reviews

Nuclear Magnetic Resonance (NMR) Imaging. By C Leon Partain, A. Everett James Jr, F. David Rollo and Ronald R. Price, pp. xxvi+552, 1983 (W B Saunders & Co., Philadelphia), £66.75.
ISBN 0-7216-7098-9

The first international clinical NMR imaging Symposium was held at Vanderbilt University School of Medicine, Nashville, on October 26-27, 1980 This book is an effort by the editors to include the subjects identified at the Symposium, as well as a number of additional developments. The authors of each section were given the opportunity to expand and develop their assigned topic.

The book is divided into eight sections which describe in turn the historical background, the theory of physical principles, technology and systems engineering, clinical results, benefits and risks, current research and development and a review of the future There is a useful glossary.

All of the authors are acknowledged experts in their field and, without exception, have produced clear and constructive contributions Some of the clinical material is inevitably dated but some chapters have a permanence which make this a useful book to possess

There is no doubt that conferences on nuclear magnetic resonance are coming thick and fast and that proceedings based on these meetings are often low key and out of date when they appear. The value of this particular collection lies in its comprehensive coverage, its high quality of review, its multidisciplinary character and its recording of an historic event. The neck tie produced for this meeting is now a collector's piece.

At a cost of almost £70 this is unlikely to be the first choice for an NMR textbook, but worth having for reference if finance permits

I. ISHERWOOD

Nuclear Magnetic Resonance Imaging–Basic Principles. By Stewart W. Young, pp. xii+163, 1983 (Raven Press, New York), $24.00

Nuclear magnetic resonance is assuming an increasing importance in the field of diagnostic medicine and there is a real need for a clear scientific dissertation on basic concepts for the beginner. Dr Stewart Young, of Stanford University, has attempted in this slim volume of 150 pages to present these concepts in a manner suitable to the whole range of disciplines which might be concerned

Clerk Maxwell, in 1870, said that "scientific truth should be regarded as equally scientific, whether it appears in the robust form of vivid colouring of the physical illustration or in the tenuity and paleness of a symbolic expression". Unfortunately, in the allocated space of this book science is sketchy whilst the numerous analogies, chosen to illustrate many of the physical concepts, sometimes stretch the mind and credulity of the reader further than the principles themselves.

There are chapters which deal separately with concepts of principles and reconstruction techniques whilst others are concerned with the components of the NMR signal and their effects on image contrast. Some clinical applications are considered. A review of available scanners is now somewhat outdated though there are useful generalisations on environmental aspects and site planning A glossary of terms is included

It would be true to say that this is an ambitious attempt to provide something for all disciplines, though, most readers, one suspects, might crave for more detail in their own field of interest This reviewer found the numerous typographical errors distracting and the standard of English in some sections quite painful

I. ISHERWOOD

Clinical Magnetic Resonance Imaging. Ed by A. R Margulis, C B Higgins, L. Kaufman and L. E. Crooks, pp xiv+342, 1983 (Radiology Research and Education Foundation, San Fransisco), £87.00

This is a book of 342 pages written by 33 authors from the University of California and San Fransisco

It starts by devoting five chapters to technical considerations outlining the physical principles, imaging techniques, NMR instrumentation and NMR tissue characterisation. There then follow 11 clinical chapters, commencing with the brain and working down through the nasopharynx, neck, chest, abdomen and ending with the musculoskeletal system. The last four chapters cover contrast media, safety, siting and economic considerations

Several points are worth making regarding this book. The first is the date of publication. This is 1983 and, therefore, most of the book would appear to be at least 2 years old The second is the price Even though the cost of illustrating books is very high, particularly in the imaging specialties, the price of nearly £90 still appears rather prohibitive. The third point is the undoubted preference of the authors at the time of writing for the spin-echo sequence. This is clearly evident in the first few pages of the book where, on one page, two images are shown, one an inversion recovery and the other a spin-echo. The conclusion which is drawn from these images is that since the inversion recovery image does not show the lesion it is inferior to the spin-echo sequence, which does. The less apparent point is that these two images have been obtained at slightly different anatomical levels, which may also account for the non-visualisation of the lesion.

The chapters outlining the physical principles and instrumentation have been well written and explain this complex subject clearly The sections on clinical imaging have also been well written and illustrated but do reflect the authors' preference for spin-echo.

In conclusion this is a good book which can be recommended but there are several reservations regarding price, the date of publication and the preference for the spin-echo pulse sequence.

DAVID KEAN

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Comparison of radiosensitivities of human autologous normal and neoplastic thyroid epithelial cells

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ABSTRACT

Studies were conducted to examine differences between the radiosensitivities of normal and neoplastic epithelial cells of the human thyroid. Freshly excised thyroid tissues from the tumours of eight patients with papillary carcinoma (PC) and five with follicular adenoma (FA) were cultured *in vitro* separately from normal thyroid tissue obtained from the surgical margins of the same patients. Plating efficiency of unirradiated control tissue was lower, on average for tumour tissue compared with normal tissue. Radiosensitivity, measured by the 37% inactivation dose D_0, was greater for carcinoma tissue than for normal tissue in seven out of eight PC cases. Adenomatous tissue was less radiosensitive than normal tissue in four out of five FA cases. This is the first report comparing the radiosensitivity of autologous normal and abnormal epithelial tissue from the human thyroid.

The efficacy of radiotherapeutic treatment of tumours is based on the relatively greater destruction of neoplastic cells amid normal tissue. The recent development of techniques for the *in vitro* culture of freshly excised human tissue has made possible the study of the relative radiosensitivities of normal and abnormal thyroid epithelial cells. Non-cycling, differentiated tissue, removed from the thyroid during surgery, is grown in culture and induced to proliferate. Growing populations of cells are exposed to ionising radiation and evaluated for their reproductive capacity. However, manipulation of cells in culture can have profound effects on cellular radiosensitivity. The series of examinations reported here eliminate one well established source of variability—individual variation of response. Autologous tissue samples from normal and abnormal regions of human thyroids were examined for differences in their radiosensitivity.

MATERIALS AND METHODS

Tissues from 13 patients undergoing partial or total surgical resection of the thyroid for either papillary carcinoma (PC) or follicular adenoma (FA) were used in the study. Normal tissues from the margins of the excised tumours were removed and cultured separately from, but under conditions identical to, those of the tumour cells. The culture method and verification of epithelial cells are described in detail elsewhere (Miller et al, 1985). Briefly, tissue was minced and digested with collagenase. The cell suspension was passed through a coarse nylon filter (53 μm average pore size), centrifuged and then plated at high density (approximately 1×10^5 cells per 35 mm dish) into culture vessels. A special mixture of culture medium, consisting of equal parts Hams F-12 and α minimum essential medium with 2.5% fetal bovine serum by volume, glucose (1.5 g/l) and six growth promoters including insulin (10 μg/ml), hydrocortisone (20 ng/ml), transferrin (5 μg/ml), glycyl-l-histidyl-L-lysine acetate (10 ng/ml), somatostatin (10 ng/ml) and epidermal growth factor (10 ng/ml), was used throughout the experiment. Penicillin (100 IU/ml) and streptomycin (100 μg/ml) were added to reduce contamination. Cells in primary culture were trypsinised (0 1% trypsin for 5 min) approximately 18 h before irradiation and plated into four 60 mm-diameter culture dishes per treatment group at concentrations which, after accounting for the plating efficiency (PE) and the lethal effects of radiation, were predicted to yield about 40 clonogenic cells per culture dish. Exponentially growing cells were irradiated at room temperature with a Softex X-ray unit operated at 40 kVp, 5 mA with 0.2 mm aluminium external filtration and a dose-rate calculated to be 770 cGy (rad) per min. Immediately before the irradiation, all but 0.5 ml of medium was discarded from each dish to facilitate irradiation with the soft X rays. After irradiation, the dishes were replenished with fresh medium. The same procedure, but without exposure to X rays, was followed for the control dishes. Medium was replenished after one week. Preliminary experiments in this laboratory indicate a relative biological effectiveness (RBE) of 1.2 for thyroid cells irradiated under these conditions, relative to ^{60}Co γ rays. After a 2-week incubation period in a humidified, 37°C incubator with 5% CO_2 and 95% air, the cells were stained with Giemsa and macroscopic colonies were counted.

For two FA patients, experiments with both normal and FA cells were carried out in duplicate, and triplicate experiments were performed with the normal cells of one PC patient. All other experiments were unreplicated. Results presented by Miller et al (1985) suggest that replicate experiments performed within a

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TABLE I

PLATING EFFICIENCIES AND ESTIMATED CELL SURVIVAL PARAMETERS BY PATIENT AND CELL TYPE

	Normal cells			Neoplastic cells		
Patient	PE(%)	D_0	n	PE(%)	D_0	n
			Papillary carcinoma			
83.18	7.1	80.7±3.5*	1.6±0.3	4.1	82.4±4.5	2.0±0.5
83.34	11.2	87.3±2.6	2.3±0.4	1.6	79.3±8.8	0.8±0.3
84.03	9.8	96.8±3.4	2.8±0.4	4.2	92.1±4.9	2.7±0.7
84.21†	2.3	69.0±3.0	2.1±0.4	5.6	65.1±3.3	6.1±1.5
84.32	6.9	75.1±3.6	1.7±0.3	2.0	67.9±4.8	1.6±0.4
84.35	8.6	89.7±3.5	2.1±0.4	2.6	68.8±4.0	1.3±0.3
84.40	9.0	79.7±3.4	3.5±0.8	2.4	66.6±4.0	6.2±2.1
84.48	2.8	91.2±5.5	1.2±0.3	5.2	73.6±2.9	3.7±0.8
			Follicular adenoma			
83.02‡	19.5	111.2±1.4	1.8±0.1	0.2	165.8±11.9	1.2±0.5
83.38	5.8	85.5±3.9	3.4±0.7	8.0	112.8±4.3	2.3±0.4
83.42‡	1.6	96.9±2.8	2.4±0.3	11.4	105.1±2.5	1.9±0.2
84.31	9.5	108.5±3.9	1.0±0.1	3.1	82.3±4.2	1.5±0.3
84.38	9.9	69.3±2.7	5.1±1.1	8.3	76.9±2.2	4.1±0.6

*Survival parameter estimate ± standard error

†Results for normal cells are based on triplicate experiments.

‡Results for both normal and neoplastic cells are based on duplicate experiments.

short time generally yield consistent results. Since each group of replicated experiments described above was performed within a period no longer than 2 days, results were pooled for the present analyses.

The surviving fraction (SF) is defined as $C/(N \times \text{PE})$, where N is the number of cells exposed to a given radiation dose and C is the number of colonies observed. The multitarget, single-hit model for SF as a function of dose (D) is written $\text{SF}(D) = 1-(1-e^{-D/D_0})^n$. This was fitted to the data for each patient and cell type by estimating the cell survival parameters D_0 and n, using the method of maximum likelihood under the assumption that, at each dose D, C is a Poisson random variable with mean $N \times \text{PE} \times \text{SF}(D)$. Tests for heterogeneity of PE according to patient disease or to cell type, and tests for

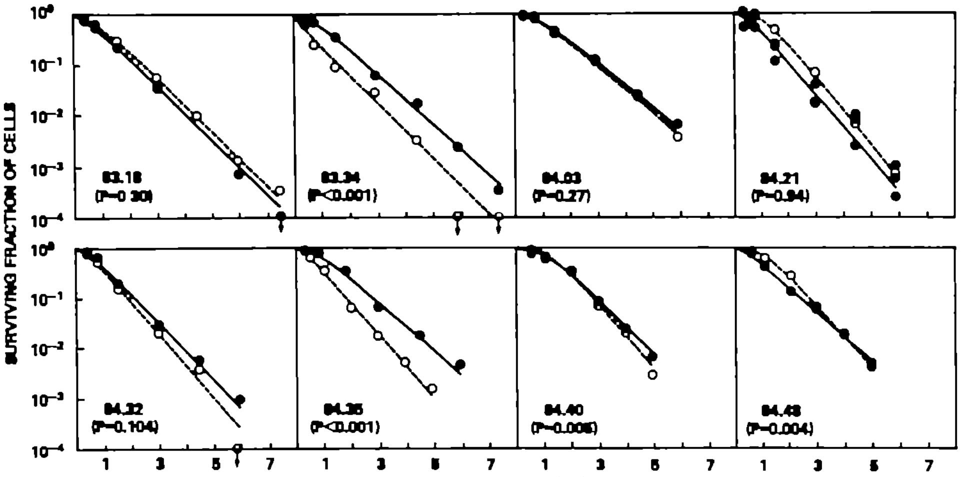

FIG. 1.

Survival of normal (solid circles and solid lines) and PC (open circles and dashed lines) cells following exposure to X rays. In each panel values of SF and fitted curves for normal and PC cells from a single patient are shown, as well as p-values for comparing the two curves. Circles with descending arrows indicate doses at which no colonies were observed.

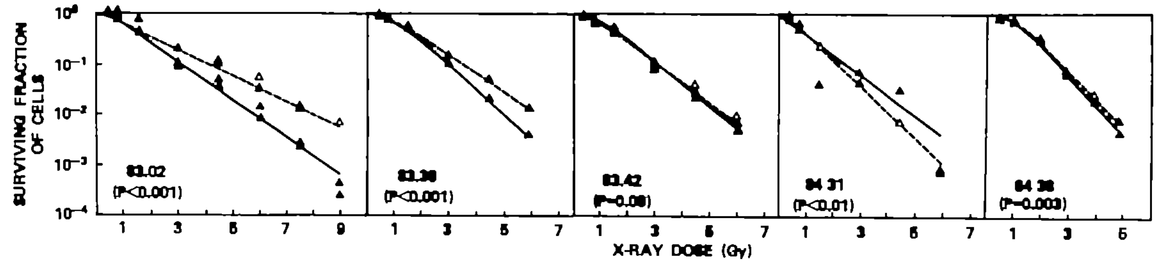

FIG. 2.

Survival of normal (solid triangles and solid lines) and FA (open triangles and dashed lines) cells following exposure to X rays. In each panel values of SF and fitted curves for normal and FA cells from a single patient are shown, as well as p-values for comparing the two curves

equivalence of each pair of cell survival curves, were based on likelihood ratio statistics (Cox & Hinkley, 1974). The statistical power of such tests in this setting is strongly dependent on the theoretical expected numbers of colonies. Therefore, the statistical significance of a difference between two survival curves depends not only on the relative positions of the curves, but also on the magnitude of colony yield.

RESULTS

The results are summarised in Table I. The values of PE for the unirradiated control dishes ranged from 0.2% to 18.5%. The PE values were all based on at least 2000 cells, so the approximate Poisson standard error for the PE from a single experiment is not greater than $0.22 \times PE^{1/2}$. Overall, the mean PE was greater for normal cells than for neoplastic cells; after adjusting for differences between subjects, this effect was highly significant (two-sided $p < 0.0001$). Essentially the same effect of cell type on PE was observed among both PC and FA patients ($p = 0.36$). However, the difference between cell types was not uniform among all patients; the PE of neoplastic cells was higher than that of normal cells for two PC patients (84.21 and 84.48) and two FA patients (83.38 and 83.42).

Figure 1 displays the cell survival curves for normal and cancerous tissue from the eight PC patients. In five patients the survival curves for the two types of cells are significantly different and in all patients but one the value of D_0 is 5% to 23% lower for cancerous tissue compared with normal tissue. For the remaining patient (83.18) the two cell survival curves do not differ significantly ($p = 0.30$) and the value of D_0 for cancerous cells is 2% greater than for normal cells.

Figure 2 displays similar results for the five FA cases. For four patients the two survival curves differ significantly and for four patients the value of D_0 is 8% to 49% greater for adenomatous patients compared with normal values. For the remaining patient (84.31) an exceptionally low surviving fraction is apparent at 150 cGy (rad) for normal tissue. However, even after deleting this point, the two cell survival curves for this patient differ significantly ($p < 0.001$) and the D_0 for adenomatous cells is 12% less than that for normal cells.

DISCUSSION

The difficulties inherent in the culturing of epithelial cells and the problems involved with obtaining appropriate surgical tissue have permitted few studies of the radiosensitivity of human epithelial cells (Mulcahy et al, 1980; Yang et al, 1983; Hiraoka et al, 1985). The data reported here indicate that neoplastic thyroid epithelial cells have significantly lower PE than normal cells from the same individual ($p < 0.0001$). However, the present findings suggest that the variation of D_0 among cell types is not simply a secondary effect induced by the variation of PE among cell types; both PC and FA neoplastic cells had, on average, a lower PE than the corresponding normal cells. However PC cells tended to have higher, and FA cells lower, values of D_0 compared with normal cells. Moreover, cells from the four patients for whom the PE of neoplastic cells was greater than normal displayed the usual pattern: lower than normal D_0 for PC cells and higher than normal D_0 for FA cells.

Our previous reports (Hiraoka et al, 1985; Miller et al, 1985) have indicated that differences between patients are the source of the substantial variability in radiosensitivity. In this report such variablity is controlled by the use of autologous normal and neoplastic cells, and the findings suggest that PC cells are generally more radiosensitive, and FA cells generally less sensitive, than normal cells, in terms of the asymptotic slope of the cell survival curve. In the absence of samples of autologous cells, it is necessary to assay cells from rather large numbers of patients in order to differentiate with any certainty the radiosensitives of various cell types Since autologous normal and neoplastic thyroid epithelial cells only occasionally become available to us, we are continuing to perform assays of unmatched samples and will shortly present results based on a large series, which will augment the current report

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Book review

Diagnostic Imaging in Hemophilia. By Holger Pettersson and Marvin S. Gilbert, pp. 142, 1985 (Springer-Verlag, Berlin), DM.145.00/approx. £39.00.

The authors of this small book have a long experience of their subject: one is a radiologist at Malmo, Sweden and the other, an orthopaedic surgeon at the Haemophilia Treatment Centre, Mount Sinai Hospital, New York. They emphasise a multidisciplinary approach and exemplify it with contributions from colleagues in medicine, surgery, haematology and nuclear medicine As a result, the text embraces a wider view of haemophilia than the title implies: overall, it is a succint review of the art of investigating and treating this disease. The progress which has been achieved already is well illustrated by the median life expectancy in Sweden: earlier this century, the severely affected died in their teens, currently, moderately severe cases achieve almost a normal life span

The effects of the disease on the skeleton and in particular the joints, as recorded by conventional radiography, are comprehensively and well illustrated. These late structural manifestations have been classified in careful detail by Dr Pettersson in a way which allows comparison of current prophylactic treatment with earlier regimes.

The majority of bleeding episodes occur within the musculo-skeletal system. Most of these can be examined safely and sequentially using ultrasound, an underestimated technique, attracting less than half the illustrations given to CT in this book. However, the critical value of the latter in pseudo-tumours, as well as in bleeds into the trunk or skull, are well displayed.

There are surprises and contentious points. Granted that arteriography is possible with factor replacement, its use is largely historic. In the case of pseudotumours, the advice to use radiotherapy if conservative measures fail would not be acceptable in all centres.

Those with a wide experience of haemophilia will find this book useful; others needing a short reference will value it even more.

J C. MACLARNON

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Accuracy of radiological staging procedures in non-seminomatous testis cancer compared with findings from surgical exploration and histopathological studies of extirpated tissue

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ABSTRACT

Preliminary and reviewed statements describing results from abdominal CT and US were compared with surgical findings and with the report from the histopathological investigation of extirpated retroperitoneal tissue.

No false positive diagnoses of retroperitoneal metastases were made by CT investigation, while US made one false positive but revealed metastases in one patient overlooked by CT.

The overall accuracies (correct answers/all patients) were 81% with CT and 80% with US (31 and 21 patients in Group I respectively).

Surgical exploration alone was no more sensitive than either of the two other methods

CT and US are highly reliable when positive but the risks of obtaining false negative results are considerable

Testicular non-seminomatous germ-cell cancer with metastases has long been considered to be an almost incurable disease. However, new treatments have been developed during the past decade that have significantly improved patient survival (Einhorn & Donohue, 1977). Nowadays, staging procedures are becoming increasingly important since the patient's clinical stage is a major factor in determining the optimal treatment regime Formerly, radiological methods for clinical staging usually included chest radiography, urography, cavography and lymphangiography.

Today this spectrum of radiological investigations has been radically altered by the introduction of computerised tomography (CT) and ultrasound (US). Both cavography and urography can be replaced by or included in the CT examination. The use of lymphangiography is declining throughout the world and as a result of the increasing accuracy of CT and US, many cancer centres have now entirely omitted lymphangiography. Chest radiography, abdominal CT and ultrasound are the only necessary radiological staging procedures at present. All the patients in the series with testicular teratomas to be presented underwent CT and most also underwent US. A minority also had bipedal lymphangiography and some were subjected to testicular phlebography.

This investigation was conducted to evaluate the accuracy of the present routine examinations for these types of staging procedures.

PATIENTS AND METHODS

Forty-eight patients (mean age 32 years, median age 29 years) were found to have testicular non-seminomatous germ-cell cancer at orchidectomy during 1978–1983 CT was conducted on all patients using a fast scanner (4.8 s) recording 12 mm thick slices every 24 mm from the diaphragm to the symphysis. Prior to this, the patient was given a 1000 ml oral dose of dilute Gastrografin (35 ml diluted in 965 ml water). Lumbar glands > 15 mm diameter and pelvic glands > 20 mm diameter were considered pathological. All CT examinations were reviewed without knowledge of the histopathology reports. Thirty patients were also examined by ultrasound static equipment (EDP 1000), later in combination with dynamic sector scanners (Autosector Technicare, DRF 12 Diasonics) Scans were performed transversely every 2 cm from the umbilical region and upwards. Longitudinal scans were made each cm covering the liver as well as the retroperitoneum from right to left. Lately, improved ultrasound equipment has also allowed us to examine the pelvic nodes.

Bipedal lymphangiography was performed on 15 patients and phlebography of the spermatic vein by selective catheterisation was undertaken in nine patients (Forsberg et al, 1981).

The patients were divided into three groups, according to their clinical stages, which dictated specific therapeutic regimes. The first group (31), were all in clinical stages (CS) I and IIA-B according to Peckham et al (1979) and all had retroperitoneal lymphadenectomies done a few days after the clinical staging procedures. In all 31 cases, microscopic examination of the retroperitoneal nodes was unaffected by the treatment.

In Group II (13 patients), CS IIB-CS IV chemotherapy (cis-platinum, vinblastine, and bleomycin) was administered according to Einhorn and Donohue (1977), before retroperitoneal lymphadenectomy. Consequently, the microscopic examination of the retroperitoneal glands in this group was influenced by chemotherapy.

In Group III (four patients), all patients exhibited CS IV with lung metastases but without any demonstrable abdominal metastases. Chemotherapy was the only treatment used on these patients and thus there is no histological verification of their metastases and they are not mentioned further in this study.

RESULTS

Original and reviewed statements of abdominal CT were compared with the surgeon's findings at retroperitoneal lymphadenectomy and with the pathological stage (PS) report from the histopathological investigation of extirpated tissue (Table I). In the 31 patients in Group I, CT gave a true negative in 20 out of the 26 patients judged to be free from metastases. CT correctly identified metastases in five patients, three of which were less than 2 cm, *i.e.*, CS IIA, and two between 2 and 5 cm, *i.e.*, CS IIB. Two of the five metastases were not detected until the CT discs were reviewed.

According to the histopathological examination of extirpated tissue, CT was unable to reveal metastases in six patients. Three metastases were less than 2 cm diameter, *i.e.*, PS IIA, while another three were between 2 and 5 cm, *i.e.*, PS IIB. During the retroperitoneal lymphadenectomy the surgeon was unable to detect any metastases in five of the six patients in PS IIA, while he could detect metastases in three of the five patients in PS IIB.

No false positive diagnosis of retroperitoneal metastases was made with CT. Calculations show that sensitivity (CT pos/true positives) = 45%, specificity (CT neg/true negatives) = 100%, and accuracy (correct answers/all patients) = 81%. Of the 26 negative CT scans, six patients had metastases, indicating a false negative rate of 23%.

Twenty-one of the 31 patients in Group I were examined by US. Eighteen were classified as CS I, two as CS IIA and one as CS IIB. According to the histopathological examination, 16 patients, including one false positive, remained in PS I, while two were classified as PS IIA and three as PS IIB (accuracy = 80%). US made one false positive diagnosis but revealed metastases in one patient which were not detected by CT until the discs were reviewed. During the operation, palpation did not indicate any metastases in three of the five patients who actually did have metastases.

Eleven patients underwent lymphangiography. This method revealed three metastases while histopathology revealed another two. Since autumn 1982, however, no lymphangiography has been done with these groups of patients in our departments.

TABLE I

COMPUTERISED TOMOGRAPHY

31 patients	Stage I	Stage IIA	Stage IIB
CS based on CT original report	28 (1*)	2	1
CS based on CT revised report	26	3 (1*)	2
Metastases disclosed by surgeon	—	1	3
PS based on histopathology	20	6	5 (1*)

(1*) = Metastases reported by US but not detected by CT until revised report.

TABLE II

ULTRASONOGRAPHY

21 patients	Stage I	Stage IIA	Stage IIB
CS based on US	18	2 (1*) (1**)	1
Metastases disclosed by surgeon	—	—	2
PS based on histopathology	16 (1**)	2	3 (1*)

(1**) = False positive.

TABLE III

LYMPHANGIOGRAPHY

11 patients	Stage I	Stage IIA	Stage IIB
CS based on lymphangiography—original report	8	2	1
Metastases disclosed by surgeon	—	1	2
PS based on histopathology	6	2	3

TABLE IV

SPERMATIC VEIN PHLEBOGRAPHY

5 patients	Stage I	Stage IIA	Stage IIB
CS based on phlebography original report	5	—	—
Metastases disclosed by surgeon	—	—	—
PS based on histopathology	2	1	2

Five patients underwent spermatic vein phlebography. Histopathology revealed metastasis in three of them. However, all were missed by phlebography and neither were they observed by the surgeon. Spermatic vein phlebography has not been conducted during the past five years at our hospital.

In Group II (13 patients), histopathological confirmation of metastases was made after chemotherapy followed by surgery. Some patients had only fibrosis and necrosis while others had mature teratomas, and a few had viable tumour cells left in the retroperitoneal

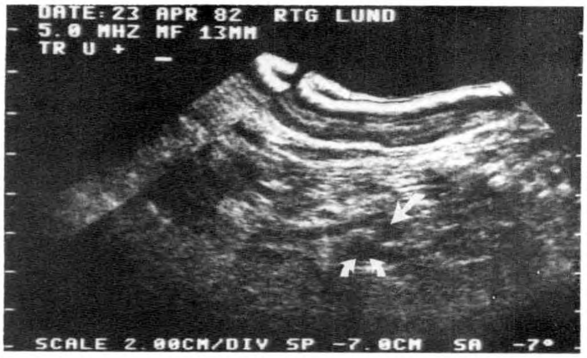

FIG. 1.

Ultrasound examination, transverse scan 7 cm cranial to the umbilicus with a rounded, echo-poor lymph node (large arrow) ventrolateral to the left of the aorta (two small arrows). Normal lymph nodes have a high echogenicity and are not visualised by US in the para-aortic area.

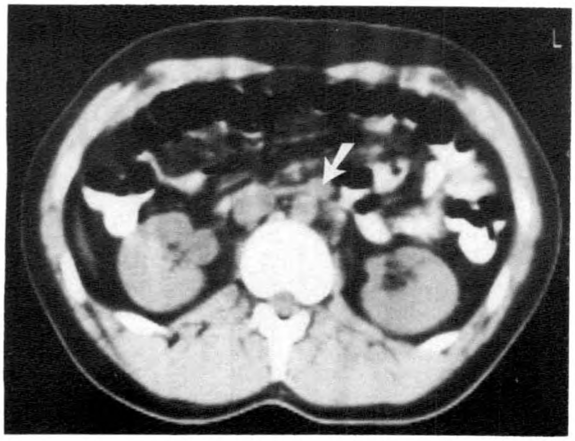

FIG. 2.

Computed tomographic examination with a lymph node within normal size (arrow). This is the same patient as in Fig. 1.

mass. However, remnants of pre-existing metastases were detected in all of these patients. According to abdominal CT, all 13 patients suffered primarily from retroperitoneal metastases (two were not detected until the discs were scrutinised) and five also had pulmonary metastases (CS IV).

Nine patients in Group II were staged by ultrasonography and in all but one, metastases were indicated.

In one patient US revealed metastases which were overlooked in the preliminary CT statement. Four patients underwent spermatic vein phlebography, three of which revealed metastases, while the fourth did not; *i.e.*, it was false negative.

Of four patients subjected to lymphangiography, metastases were indicated in three (thus one false negative).

DISCUSSION

The overall accuracy of CT in the two groups investigated, totalling 44 patients, was 83% as substantiated by microscopic examination of retroperitoneal lymph nodes. These figures were taken from a review study; in the original reports, four misinterpretations led to a somewhat lower clinical accuracy. Another Swedish CT investigation (Magnusson et al, 1982) of 29 patients reported similar accuracy (82%). In the difficult-to-detect stage IIA, which has an upper metastatic size limit of 20 mm diameter and also includes all normal-sized nodes involved with cancer, Magnusson et al had only one false negative in six cases, while three of six cases were missed in our study. Comparing false negative rates, we found 26% (7/27) while Magnusson et al reported 13%, Richie et al (1982), 44%; while Lien et al (1980) had 40% false negative CT scans in their group of patients. These results reflect the obvious problem: It is difficult or next to impossible using CT or ultrasound to determine if normal-sized or nearly normal-sized lymph nodes in the retroperitoneum are harbouring cancer cells.

In our study it was not possible to detect all metastases by inspection and palpation during surgical exploration. It is obvious from these results that surgical exploration alone is not more accurate than abdominal CT. To obtain increased accuracy, surgical exploration must be combined with multiple frozen sectioning. If negative, this unilateral procedure preserves the ability to ejaculate in most men (Cavallin-Ståhl et al, 1981; Fosså et al, 1984; Ous, 1983).

Reviewing the overall CT accuracy from the literature we find: Richie et al (1982), 73%; Magnusson et al (1982), 82%; Rowland et al (1982), 68%; Williams et al (1980), 87%; as compared to 83% in our study. At present these results can be considered as good as the method permits and are second only to a histological examination after lymphadenectomy. Since 10–20% of the patients in PS I eventually relapse, histopathology is not always accurate either. To achieve 100% accuracy, serial sectioning of all extirpated tissue would have to be done but this is impossible by practical means. Note that our CT results were obtained from patients who were young, often lean, with little retroperitoneal fat, and with 12 mm space between slices. It should be emphasised that there are strict limitations on the sensitivity, specificity and accuracy of both CT and US. A microscopic cancer deposit in a normal-sized gland cannot be detected by radiological methods or by palpation. Nevertheless, a failure by CT or US to detect such a metastasis is judged as a false negative although the methods have never been claimed to replace a microscope. Several of our patients had only microscopic metastases. Furthermore, the TNM classification (UICC, 1978) uses the longest diameter of a lymph node as the determinant parameter, while CT measures only the transverse diameter. A gland might very well be less than 15 mm in transverse diameter and more than 20 mm in longitudinal diameter, PS IIB by TNM standards, while CT would report a CS I. As is well known, retroperitoneal nodes are as a rule elongated in the craniocaudal direction with their transverse diameters being the shortest. Fortunately, the capacity and resolution of CT are continuously improving, enabling an increase in the quality of the examinations, *e.g.*, consecutive slices at least in the kidney areas.

At our institution, lymphangiography has been downgraded among the radiological staging methods, partly because of its invasiveness and time-consuming nature and partly for economic reasons; nevertheless, it may sometimes reveal metastases in non-enlarged nodes (Ekelund et al, 1980; Lien et al, 1983).

Overall, ultrasound examination has a reported accuracy in the same range as CT in this context (Burney & Klatte, 1979; Rowland et al, 1982; Williams et al, 1980). It is also a good method of examining the retroperitoneum, but has certain limitations in the pelvic area due to interfering bowel gas, and sometimes also in the kidney region. In spite of these difficulties it is possible to obtain acceptable accuracy with US; in our centre therefore, it has been used to complement CT during follow-up examinations. Today, our department always does an ultrasound examination of the testes prior to orchidectomy while the abdomen is investigated at the same time (Forsberg & Olsson, 1983). This seems to be a reasonable approach since it is apparent from this study that US can reveal metastases overlooked by CT.

Radiological staging of testicular cancer patients utilising CT and US can thus be considered highly reliable when results are positive. However, when no metastases are found the risk of false negative results is considerable.

ADDENDUM

The latter $\frac{1}{3}$ of these patients are included in the material of Swenoteca—Swedish and Norwegian testicular cancer project.

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Angiography in transient cerebral ischaemia using three views of the carotid bifurcation

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ABSTRACT

A prospective study was made of 135 patients having cerebral angiography for suspected carotid atheroma. The aim was to assess the value of a technique in which selective injections were used to show the origins of the vessels from the aortic arch and three views were taken of each of the carotid bifurcations.

Disease was frequently asymmetrical and was shown in only one of the three views of the carotid bifurcation in 44% of 181 patent atheromatous internal carotid arteries. Atheroma was seen on a single view significantly more often ($p < 0.01$) than was complicated atheroma, indicating that the technique was showing more early lesions than would be seen with fewer views of the region. Disease was not shown significantly more often in any one particular view, so that all three are essential to examine the bifurcation completely.

The occurrence of a transient ischaemic attack has serious implications for the patient in whom it occurs. Some 60% of patients having one will have a stroke within five years (Machleder, 1979), and 51% of the strokes will occur within a year of the attack (Whisnant et al, 1973). The possibility of preventing a stroke by endarterectomy in those patients with stenosis or ulceration of the internal carotid artery (Eastcott et al, 1954) or of increasing cerebral blood flow in those with occluded internal carotid arteries by anastomosing the superficial temporal to the middle cerebral artery (Yasargil et al, 1970) has made accurate diagnosis of extracerebral arterial disease important.

The accuracy of angiographic diagnosis has been questioned following the study in two planes of radiographed casts of carotid bifurcations (Croft et al, 1980) and the comparison of ulcers found at operation with those reported at angiography (Edwards et al, 1979). It has been shown in experimental work on radiographs of filling defects in tubes that three views of a tubular structure are needed to record the degree of narrowing of the tube accurately (Berne et al, 1970), and on the basis of experimental studies of casts of the internal carotid arteries we concluded that a lateral and two oblique views of the carotid bifurcation gave good visualisation of asymmetrical lesions of the area (Jeans et al, 1983). We have now assessed prospectively the value of routinely taking three views of the carotid bifurcation in a group of patients having angiograms for suspected extracerebral atheroma.

PATIENTS

Clinical and angiographic findings were recorded in a prospective study of 135 patients who had angiography for suspected carotid atheroma over a three-year period. The patients were selected for angiography from a larger symptomatic group when they were found to have abnormal Doppler ultrasound studies or bruits in the neck on examination. The principal presenting symptom was a transient ischaemic attack in 66 (49%), amaurosis fugax in 44 (33%), and a stroke with recovery in 19 (14%) patients. In six (4%) patients an incidentally discovered carotid bruit led to investigation.

There were 104 (77%) men and 31 (23%) women, and most were aged between 50 and 69 years (Fig. 1). The majority of the patients had symptoms or signs of disease in other parts of the vascular system (Table I).

METHODS

Patients were catheterised from a femoral approach using a 'headhunter', Mani or 'sidewinder' catheter. The subclavian, brachiocephalic and carotid arteries were selectively catheterised and films were taken of:

(a) The left subclavian artery. The head was turned to the right, and 10 ml of contrast medium injected with the catheter at the mouth of the artery.

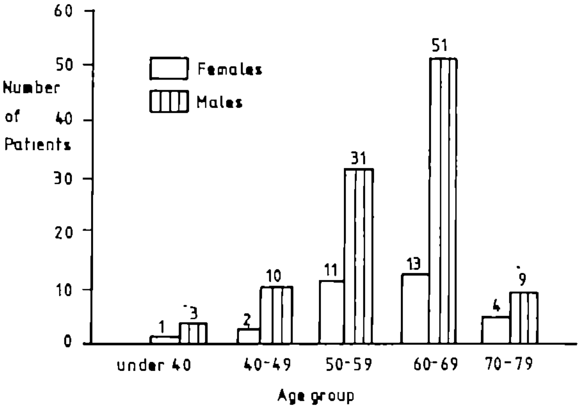

FIG. 1

Age and sex distribution of 135 patients investigated

TABLE I

VASCULAR AND RELATED BIOCHEMICAL ABNORMALITIES FOUND IN PATIENTS STUDIED

Heart disease	46 (34%)
Previous infarction	33 (24%)
Mitral or aortic valve disease	13 (10%)
Hypertension	
Being treated	47 (35%)
Diastolic >99 mm Hg	31 (23%)
Vascular disease of legs	40 (30%)
Diabetes	11 (12%)
Raised plasma lipids (measured in 92)	49 (53%)

(b) The brachiocephalic artery. The head was turned to the left and the right shoulder raised; 10 ml of contrast medium was injected with the catheter at the mouth of the artery.

(c) The carotid arteries. The head was turned first towards the side being injected ('the soft tissue oblique'), then to the opposite side so that the artery was positioned over the cervical spine ('the bone oblique'). A lateral film was then taken with the head straight using a horizontal beam (Fig. 2). Each film was taken during an injection of 5 ml of contrast medium, and about 1 ml was injected during positioning to ensure that the origins of the internal and external carotid arteries were separated (Fig. 3).

(d) The cerebral vessels on the side appropriate for the patient's symptoms were shown on lateral and AP projections in arterial, capillary and venous phases following an injection of 8 ml of contrast medium into the common carotid artery. If an internal carotid occlusion was found appropriate films were taken to show any extracerebral collateral blood supply to the cerebral arteries.

(e) A single lateral film of the opposite carotid siphon was taken using 5 ml of contrast medium.

Initially the contrast medium used was meglumine iothalamate (Conray 280), followed by ioxaglate (Hexabrix) and iopamidol 300 (Niopam) as these became available. Single films of the extracerebral vessels were taken at each injection initially, and more recently 105 mm films have been taken using two films per second for two seconds with an IGE L-U arm apparatus.

Disease of a vessel was classified as:

(a) *Atheroma*—when there was a smooth or irregular filling defect in the margin of the column of contrast medium, without narrowing. This was usually situated in the carotid bulb (Fig. 4).

(b) *Complicated atheroma*—when there was
  i) a stenosis, seen as a narrowing of the outline of the column of contrast medium in relation to the outline more distally. The degree of narrowing was expressed as a percentage of the width of the distal vessel (Figs. 5 and 6).
  ii) an ulcer, seen as a protrusion of contrast medium in the presence of atheroma (Fig. 7).
  iii) a combination of both ulcer and stenosis.

(c) *Occlusion* of a vessel, when the expected vessel outline was not shown.

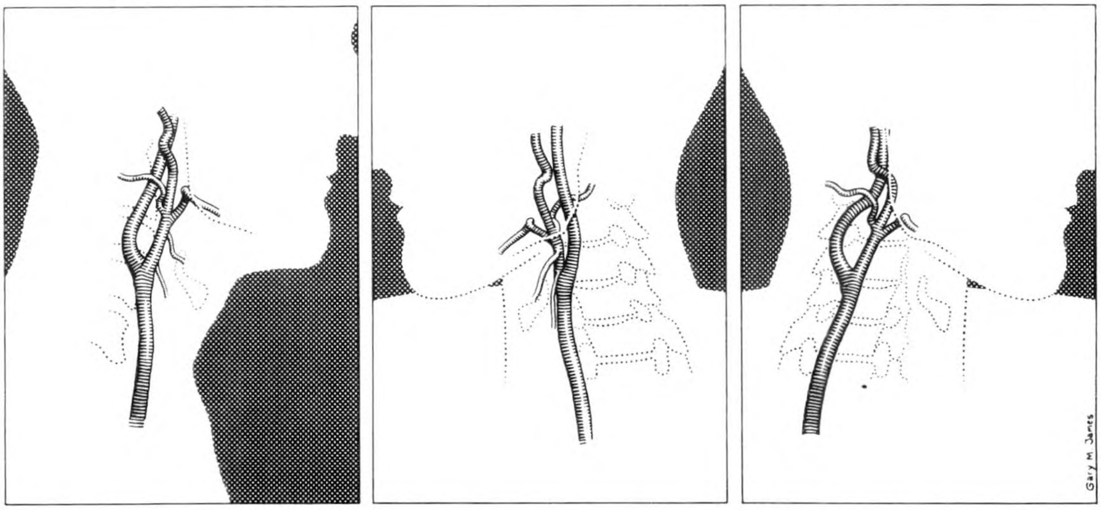

FIG. 2.

Diagrammatic illustration of the views taken of a right carotid bifurcation. From left to right: horizontal beam lateral, 'soft tissue' and 'bone' obliques.

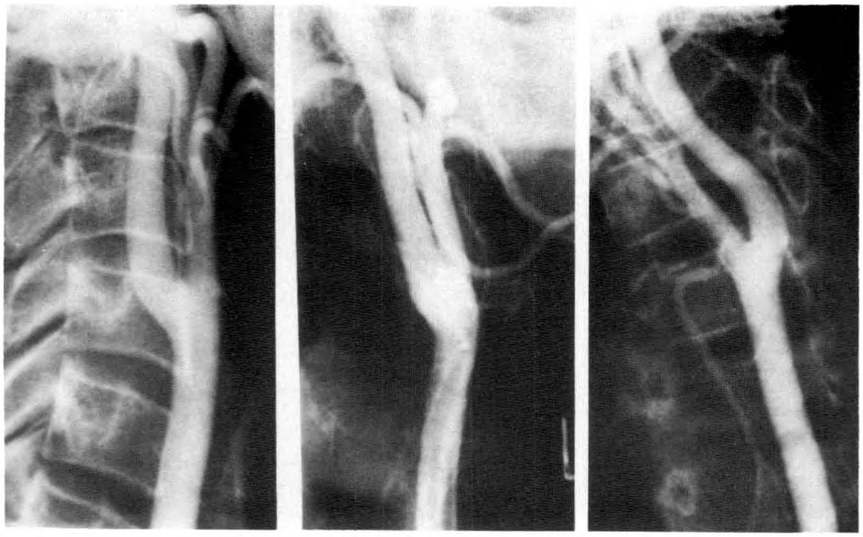

FIG. 3.
Normal left carotid bifurcation. From left to right: Horizontal beam lateral, 'soft tissue' and 'bone' obliques.

RESULTS

Extracerebral vascular disease

Atheroma was present in the brachiocephalic or subclavian arteries in 67 (25%) and in the common carotid in 56 (21%) vessels, with ulceration in a further 7 (3%). Two other common carotid arteries were occluded. The external carotid artery origin was atheromatous in 69 (26%), and the internal carotid origin (analysed in more detail below) abnormal in 198 (73%). Kinks or coils were seen in the internal carotid in

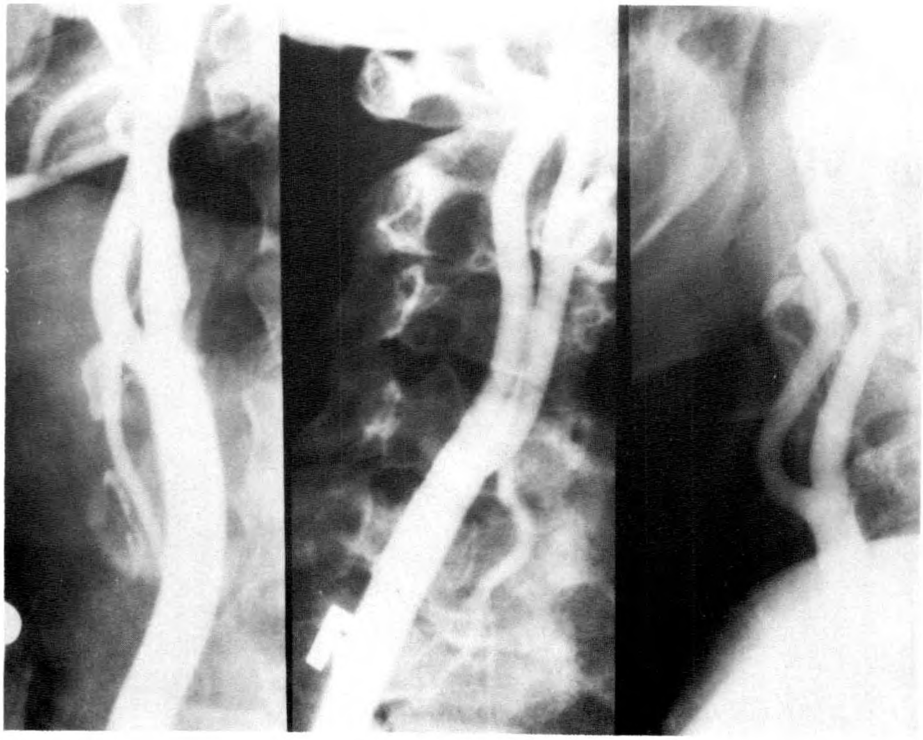

FIG. 4.
Atheroma: a plaque is shown on the 'soft tissue' oblique. The width of the artery at the narrowest point is the same as that beyond the bulb.

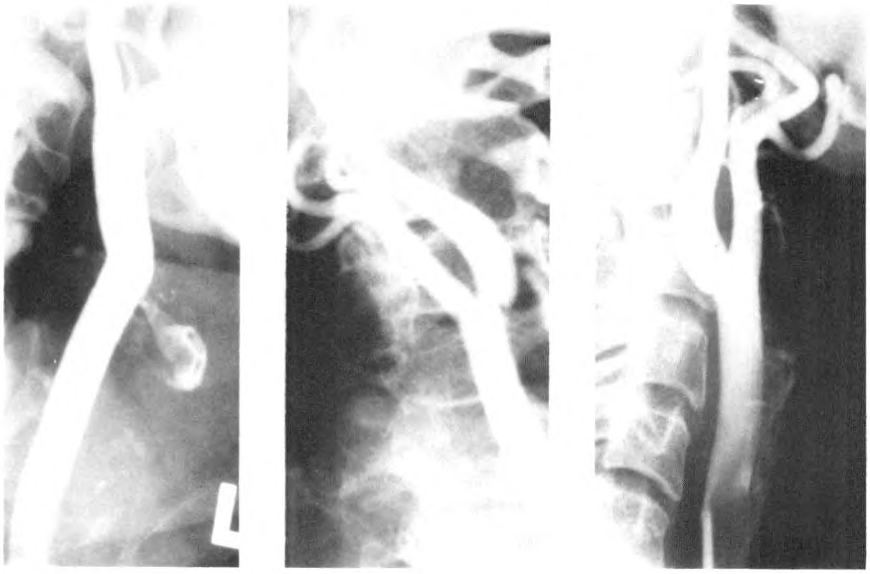

FIG. 5.

Complicated atheroma: an atheromatous ridge causing a less than 50% stenosis is seen only on the 'bone oblique' view.

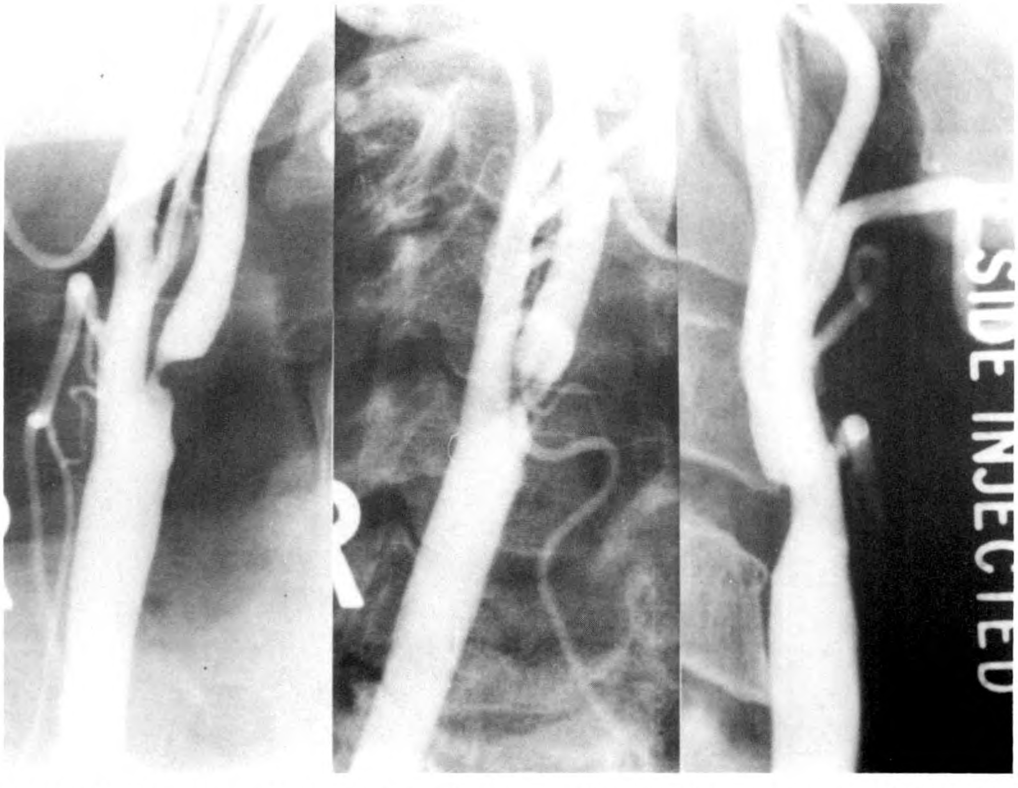

FIG. 6. Complicated atheroma: critical stenosis of right internal carotid artery. Disease is shown on all three views, but the stenosis is clearly seen only on the 'soft tissue' oblique.

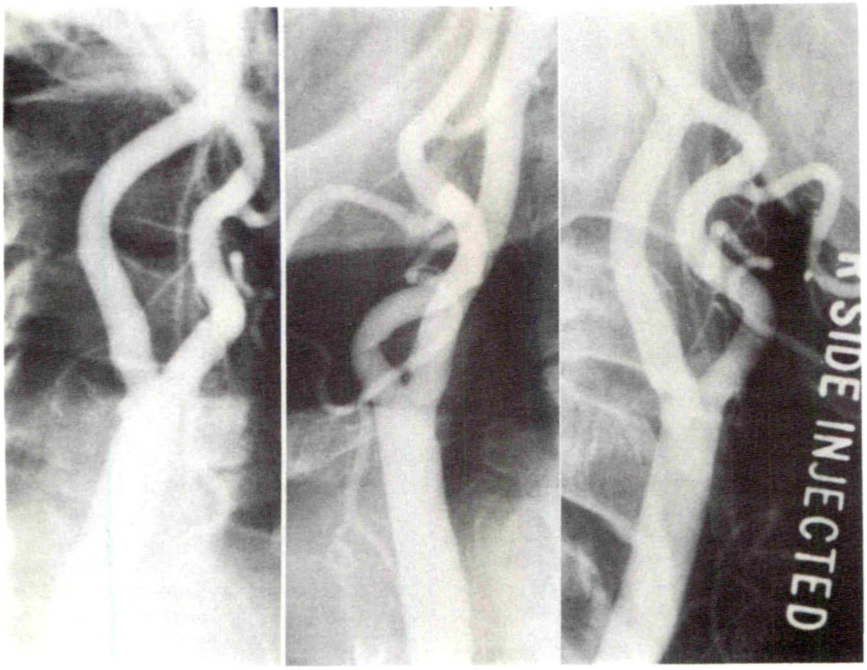

FIG. 7.

Complicated atheroma: an atheromatous plaque is seen on the 'soft tissue' oblique, and an ulcer is seen on the 'bone' oblique.

35 (13%) and the carotid siphon was atheromatous in 37 (14%) vessels. A stenosis was seen at the origin of 47 (17%) vertebral arteries.

Internal carotid artery origin disease

Two common carotid arteries were occluded, and three carotids on each side were not examined when the clinically relevant side had been shown, and catheterisation was difficult or prolonged. Only 16 (12%) patients had radiologically normal carotid arteries on both sides. The 198 (76%) abnormal carotids of the 262 examined showed atheroma alone in 64 (24%), atheroma with ulceration in 30 (11%), and atheroma with stenosis either with or without ulceration in 87 (33%). Seventeen (6%) internal carotid arteries were occluded, one patient having both sides affected.

Bifurcation view showing disease. (Tables II, III)

Less severe disease was seen significantly more often in one view than in two or three when compared to complicated atheroma ($p < 0.01$, $\chi^2 = 10.22$, 1 d.f., excluding occluded arteries). Although the presence of severe disease might be apparent in all three views, detail was often seen clearly in one view only (Fig. 6), and occasionally each view showed a different appearance (Fig. 8). No one of the three views used showed disease significantly more often than any other.

TABLE II

RELATIONSHIP OF NUMBER OF VIEWS OF CAROTID BIFURCATION SHOWING DISEASE TO THE SEVERITY OF THE DISEASE SHOWN. (17 OCCLUDED INTERNAL CAROTID ARTERIES EXCLUDED)

	Bifurcation disease shown on			
	1 view only	2 views only	All 3 views	Total
Atheroma	39 (61%)	21 (33%)	4 (6%)	64 (100%)
Complicated atheroma	41 (35%)	49 (42%)	27 (23%)	117 (100%)
Total	80 (44%)	70 (39%)	31 (17%)	181 (100%)

Atheroma is seen significantly more often on one view than is complicated atheroma.
($p < 0.01$, $\chi^2 = 10.222$, 1 d.f.)

TABLE III

VIEW SHOWING DISEASE IN 80 CAROTIDS IN WHICH DISEASE WAS SHOWN IN ONE VIEW ONLY

	View showing disease			
	'bone oblique'	'soft tissue oblique'	lateral	Total
Atheroma	14 (36%)	10 (26%)	15 (38%)	39 (100%)
Complicated atheroma	12 (29%)	12 (29%)	17 (42%)	41 (100%)
Total	26 (33%)	22 (27%)	32 (40%)	80 (100%)

No one view shows disease significantly more often than another.

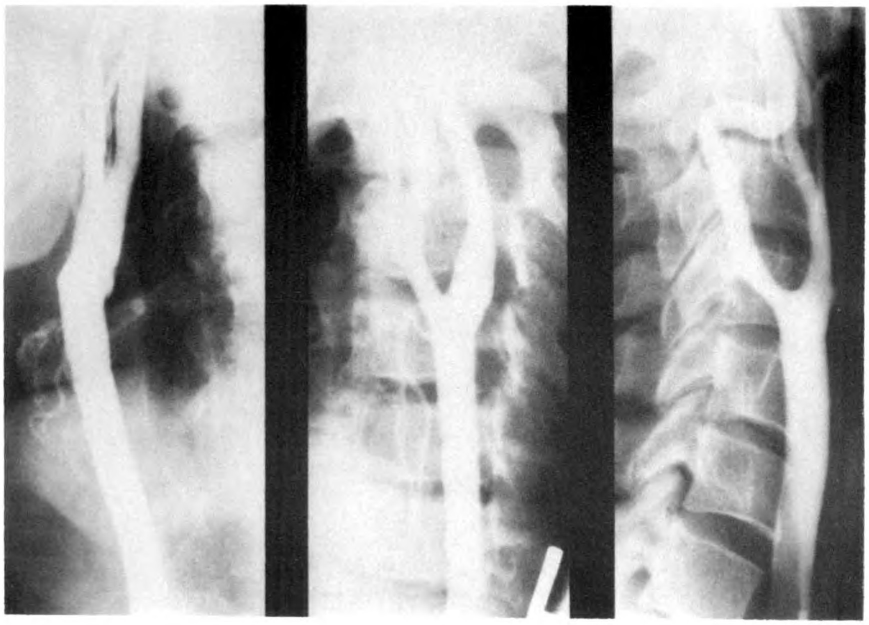

FIG. 8.

Complicated atheroma: an ulcer is shown on the 'soft tissue' oblique, with a normal appearance on the 'bone oblique'. The lateral view shows a stenosis at the origin and a 'kink' distally in the internal carotid.

Relationship of disease found to clinical presentation. (Table IV)

Disease was found equally often on the clinically affected and unaffected sides, both in patients with hemisphere and visual symptoms. A bruit was found in 75 (28%) carotids on examination, and 69 (92%) of these showed disease on angiography. Two patients had intracerebral lesions. In one with normal carotids a glioma was found, and in one with atheroma on the appropriate side there was a meningioma.

Complications and treatment

There was no complication in 105 (78%) patients. In 19 patients there was an appreciable haematoma at the puncture site. Six patients had a temporary neurological deficit, which lasted less than 24 hours in five, and over 24 hours in one. Four patients had a neurological deficit lasting over one week. One patient died of a non-neurological cause. The total neurological complication rate was 7%, and the persistent deficit rate was 3%.

Following investigation a vascular operation was performed in 43 (32%) patients—carotid endarterectomy in 37 and an anastomosis from the superficial temporal to the middle cerebral artery in six patients. An intracerebral lesion was treated in two patients. Seventy-six (56%) were treated with aspirin, and 14 (10%) were entered into the UK trial of anti-platelet therapy.

TABLE IV

RELATIONSHIP OF INTERNAL CAROTID DISEASE TO CLINICAL PRESENTATION

	Internal carotid				
Clinical localisation	Not shown	Normal	Abnormal	Occluded	Total
Affected side	—	27	61	11	99
Opposite side	6	25	66	4	101
Other*	—	12	54	4	70
Total	6	64	181	19	270

*Symptoms poorly localised, bilateral, or vertebrobasilar.

DISCUSSION

This study has shown that examining the common carotid bifurcation with three views increases the number of lesions shown, as well as giving more information about the lesions. Selective catheterisation is necessary to opacify the bifurcation satisfactorily and careful positioning is needed to avoid obscuring the proximal internal carotid by overlying vessels. We originally used arch angiography as part of the procedure, but stopped because it increases both the time taken and the amount of contrast medium given, and means changing catheters. All these factors increase the risk of the procedure (Herlinger, 1976), and arch angiography gives little increase in useful information (Goldstein et al, 1982). We find that disease at the origins of the great vessels is satisfactorily shown by selective injections, and with the appropriate views carotid siphon atheroma and any relevant collateral cerebral circulation can be demonstrated.

The purpose of angiography is twofold: it helps to make a diagnosis to account for the presenting symptoms and also to demonstrate the extent of any disease present, so that a rational decision can be made about the best treatment for a particular patient. Should surgery be considered, the surgeon will need to know not only the extent of disease in the clinically relevant bifurcation, but also if there is disease in the carotid siphon which would make bifurcation surgery useless, if there is adequate inflow to the affected carotid system, and whether the opposite side is affected. It is apparent from this study that the opposite side is diseased as often as is the symptomatic side, and this information is necessary before making a decision about operation. Twelve percent of patients with asymptomatic lesions shown on angiography develop cerebral symptoms (Levin et al, 1980) and these patients have an increased risk of myocardial infarction during major operations (Barnes & Marszalek, 1981). A high proportion of our patients have demonstrable disease because we screen patients without bruits with Doppler ultrasound, and reserve angiography with its potential complications for those patients with abnormal Doppler examinations or bruits on the clinically appropriate side who are likely to have surgically treatable disease. Bruits are well recognised as indicators of the presence of carotid disease (Baird, 1983) and in this study 92% of the arteries over which a bruit was heard were diseased

Transient cerebral ischaemia is due either to inadequate perfusion beyond a stenotic segment, or to embolism from platelet aggregates or cholesterol crystals produced on ulcerated plaques of atheroma (Imparato et al, 1979) The episodes may be precipitated by sub-intimal haemorrhage causing elevation and ulceration of plaques or sudden narrowing of the lumen, and radiological signs associated with sub-intimal haematomas have been described, the principal one being a well circumscribed, spherical filling defect with sharp acute margins (Edwards et al, 1979). We have so far been unable to differentiate these lesions angiographically The size of ulcers is related to the prognosis for the patient, there being an annual stroke rate of less than 1% with 'small' ulcers, compared to 12% per year for large or irregular ulcers (Moore et al, 1978). The evaluation of an ulcer depends on seeing it in profile and the three views that we use are more likely to give a profile view than are one or two views. Three patients with 'minimal irregularities' of the wall shown on angiography showed no abnormality when subjected to surgical exploration (Mendelowitz et al, 1981) and it appears that these minor irregularities on angiography should not be diagnosed as being due to disease.

The reporting of stenosis of the internal carotid artery presents difficulties (Brown & Johnston, 1982) because of varying size of the carotid bulb. The assessment may be based on the visual appearance of the artery, on the width of the lumen at the lesion (Ojemann & Crowell, 1983) or on the relation of this to either the proximal (Alter et al, 1972) or the distal arterial width (Eisenberg et al, 1977). Whenever measurements are made it is difficult to allow for the normal and very variable distension of the artery at the carotid bulb, and we have seen very obvious plaques of atheroma in the bulb which were not producing a stenosis. Magnification factors will vary from one patient to another and realistic measurements are difficult if 105 mm film is used, unless a scale is introduced at angiography. A short run of 105 mm film is helpful in assessing some lesions since video and cine studies have shown that the appearance and size of lesions may alter with the degree of mixing of blood and contrast medium as well as the changing distension of the artery and carotid bulb during the cardiac cycle (Lusby et al, 1982). It seems sensible therefore to report on the visual appearance of lesions and give an approximate estimation of the percentage reduction in diameter in terms of 'less than 50%, 50–75%, greater than 75%', or 'critical' stenosis.

The presence of kinking has been defined as an angle of 90° or less between two segments of the vessel on one film (Metz et al, 1961). Those authors also defined coils as a complete loop of vessel and thought that both were normal variants since they were found at every age. Kinks have also been thought to be due to arteriosclerosis or fibromuscular hyperplasia and removal in patients with transient ischaemic attacks is said to stop attacks (Vollmar et al, 1976). A kink associated with a 50–75% stenosis was removed in one of our patients, with resolution of symptoms.

The findings in this study have a particular relevance to the use of intravenous digital subtraction angiography. Since it appears that three views of the carotid bifurcation improve the demonstration of disease to a significant extent, the use of that technique to produce the same amount of information may require an unacceptable amount of contrast medium.

CONCLUSIONS

The routine use of three views of the carotid bifurcation increases the number of angiographic abnormalities shown, and the use of selective angiography alone will demonstrate abnormalities at the origins of the major vessels, so making aortic arch angiography unnecessary. The view in which the lesion will be seen cannot be forecast, so that all three views should be done as a routine.

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Contrast media in double-contrast arthrography of the knee: a comparison of ioxaglate and iothalamate preparations

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ABSTRACT

Hexabrix (sodium and meglumine ioxaglate) is a satisfactory medium for use in double-contrast knee arthrography. It shows no advantage over the ionic medium, meglumine iothalamate, in the quality of the immediate films, but it produces significantly better coating of the meniscus in delayed films and better results in knees which have an effusion These advantages are to some extent counteracted by the fact that Hexabrix causes more pain or discomfort after the examination than meglumine iothalamate.

Double-contrast arthrography of the knee at the present time is usually performed using a conventional ionic contrast medium such as meglumine iothalamate (Stoker, 1980). This type of medium is acceptable to the patient and gives excellent results in experienced hands. However, with an inexperienced radiologist or with the occasional problem patient, the examination may be prolonged beyond the usual duration of 10–20 minutes. In this event, the medium starts to diffuse into the surface of the articular and fibro-cartilage—imbibition—(Ricklin et al, 1971), causing the articular margins to become poorly defined by the layer of contrast medium. Absorption through the synovium at the same time reduces the total amount of iodine in the joint, thereby diminishing photographic contrast still further, sometimes to the extent that the radiographs are not of diagnostic quality

The new non-ionic contrast media offer theoretical advantages over these conventional media, mainly as a result of their low osmolality. This should lead to less dilution of contrast medium in the joint space. Extrapolation from their effects on endothelium (Raininko, 1979) makes it possible to suggest that less synovial inflammation may result. Another potential advantage is the increased viscosity of all suitable preparations of non-ionic media. The more viscous liquid provides a thicker layer of contrast medium on the meniscal surface and thus offers the viewer better perception of the margin.

Dimeric contrast media offer the opportunity of doubling the concentration of iodine per molecule in solution. The only dimeric contrast medium now on the market in this country is sodium meglumine ioxaglate (Hexabrix, May & Baker); this is also a medium of low osmolality. The larger size of the molecule gives Hexabrix different physico-chemical properties and offers the possibility of further improvements in the quality and duration of coating of the joint surfaces.

The aim of the present trial was to compare sodium meglumine ioxaglate with the conventional medium, meglumine iothalamate (Conray 280, May & Baker). Both media are already marketed for use in knee arthrography.

PATIENTS AND METHODS

One hundred and five sequential patients undergoing double-contrast arthrography of the knee at the Royal National Orthopaedic Hospital were included in the trial. The patients were allocated to the ioxaglate or iothalamate group in a random fashion, according to whether their birthdays were even or odd numbers.

Arthrography was performed using the double-contrast method of Stoker (1980). Three ml of Hexabrix 320 or Conray 280 were injected into the joint. The gas used was a mixture of air and carbon dioxide, which was not removed at the end of the examination but allowed to absorb. The radiologist performing the examination recorded the quality of coating of the menisci and the degree of pain, if any, reported by the patient at the time. Any adverse reactions were also recorded

Delayed films were obtained 5–10 minutes after completion of the arthrogram in 38 randomly selected patients. The quality of coating and the amount of absorption or imbibition of contrast into the cartilage were graded.

The patients were asked to record any pain, swelling or other problems on a questionnaire which they completed and returned 48 hours after the examination.

The films of 77 patients were later assessed independently by two radiologists (D.J.S. and C.I.). The assessors were unaware of which contrast medium had been used. The quality of the examination and the quality of coating of the menisci were graded as excellent, good, acceptable or poor.

RESULTS

The age and sex distribution of the patients is shown in Table I. Of 105 patients, 89 returned the

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TABLE I

Age and sex distribution

	10–19	20–29	30–39	40–49	50–59	60+	M/F	Total
Conray	3	20	8	8	8	4	36/15	51
Hexabrix	9	16	20	7	2	0	40/14	54

TABLE III

Pain assessed by the radiologist at the time of the arthrogram

	Conray	Hexabrix
Absent	33	37
Slight	16	11
Moderate	1	6
Severe	1	0
Total	51	54

questionnaires: 45 of these had received Conray and 44 Hexabrix.

The data were analysed using the chi-squared test and, in the case of the smaller categories, two groups were added together before testing. Such categories have been bracketed in the tables.

The patients' assessments of pain immediately following and 48 hours after the arthrograms are shown in Table II. Significantly more patients reported some immediate pain in the Hexabrix group. This contrasts with the patients' reports to the radiologist at the time of the arthrogram (Table III), which demonstrated that only a minority of patients admitted to any pain and no difference was shown between the two groups. The amount of pain complained of by the patient after 48 hours was greater in the Hexabrix group, but the difference was not statistically significant, nor was the degree of swelling of the knee different in the two groups (Table IV).

Thirty-eight films from the Conray group and 39 from the Hexabrix group were assessed later by the two radiologists (Table V). No significant difference was observed in the quality of the examinations overall nor in the quality of meniscal coating between the contrast media.

Analysis of the delayed films taken 5–10 minutes after completion of the arthrogram showed significantly better delayed coating ($p = 0.0007$) and less imbibition ($p = 0.008$) in the Hexabrix group than in the Conray group (Table VI).

The patients with and without effusions over 5 ml were assessed separately on the quality of the coating recorded at the time of the examination (Table VII). No difference in quality was shown between those with and without effusions, but when quality was scored separately for each contrast medium, Hexabrix was found to give significantly better quality of coating in the patients who had effusions than did Conray ($p = 0.04$).

Any other adverse effects mentioned by the patients on the questionnaire were roughly categorised, and these replies are listed in Table VIII. Various sensations in the knee were reported. Most of these were related to the presence of gas in the joint, which made the joint feel unstable. In some patients the presenting symptoms were temporarily aggravated as a result of manipulation of the knee during screening but no obvious differences were observed between the two media.

Only one systemic reaction occurred which could be attributed to the contrast medium. This, in a patient who had received Conray, consisted of sneezing, itching and a mild urticarial rash, all of which resolved spontaneously. Contrast on the immediate films in this patient was good, indicating that the injection had not been intravascular, but the contrast medium disappeared unusually quickly.

DISCUSSION

The first available dimeric contrast medium to become available for use in arthrography was Dimer X (meglumine iocarmate solution 60%), which was subsequently withdrawn because of its complications, essentially in other fields of radiology. It had proved to be a good medium for arthrography nevertheless, as it gave film of good quality and good delayed coating (Roebuck, 1977). Hexabrix is also a dimer and it is

TABLE II

Assessment of pain/discomfort by the patients

	Conray	Hexabrix
(a) *Pain immediately after the arthrogram*		
No more uncomfortable	15	2
More uncomfortable	20	22
Painful	10	20
Total	45	44
(b) *Pain at 48 hours*		
No more painful than before	21	15
More painful than before	24	29
Total	45	44

TABLE IV

Swelling reported by the patients at 48 hours

	Conray	Hexabrix
No more swollen than before	12	8
More swollen than before	33	36
Total	45	44

TABLE V

QUALITY

	1st assessor		2nd assessor	
	Conray	Hexabrix	Conray	Hexabrix
(a) *Quality of examination*				
Excellent	19	12	15	20
Good	15	22	20	13
Acceptable	3	5	2	6
Poor	1	0	1	0
Total	38	39	38	39
(b) *Quality of meniscal coating*				
Excellent	12	14	17	22
Good	22	20	14	11
Acceptable	4	4	7	5
Poor	0	1	0	1
Total	38	39	38	39

TABLE VII

QUALITY OF COATING IN PATIENTS WITH EFFUSIONS

	With effusions		Without effusions	
	Conray	Hexabrix	Conray	Hexabrix
Excellent	1	6	10	16
Good	3	6	16	15
Acceptable	5	0	10	5
Poor	3	3	2	2
Total	13	15	38	39

reasonable to expect it to be just as effective as Dimer X.

In single contrast studies in dogs (Katzberg et al, 1976), Dimer X provided the best radiographic quality and the longest duration of diagnostic iodine levels in the joint when compared with metrizamide and various monomeric media. Johansen and Berner (1976) demonstrated that the duration of good contrast coating in the joint was longer with Dimer X than with conventional ionic monomers, though metrizamide was slightly better than the dimer.

Dimer X has been shown to give less pain, less joint swelling and slower contrast absorption than Urografin 60% (meglumine diatrizoate) in patients undergoing double-contrast knee arthrography (Roebuck, 1977) Laasonen and Lindholm (1983) confirmed that coating on delayed films was of better quality with Dimer X than with meglumine iothalamate or sodium calcium meglumine iocarmate, but the quality of the immediate films was not improved significantly.

The 'new generation' contrast media offer double the concentration of iodine for each particle in solution. All except ioxaglate achieve this by being non-ionic. The non-ionic media have certain theoretical advantages over conventional media in arthrography. They can be expected to cause less osmolar shift of fluid to the intrasynovial compartment and hence less dilution of contrast medium in the joint They are also likely to cause less synovial irritation (Belli et al, 1984). These authors also found that the theoretical advantages were not significant in clinical practice in respect of one non-ionic medium, iohexol.

Hexabrix contains the dimeric molecule ioxaglate in a mixture of its sodium and meglumine salts. The size of the ioxaglate molecule gives it two properties not shared by the non-ionic media.

(1) It is more viscous than any other medium Consequently, it can be expected to adhere more thickly to the meniscus and enable the edge to be more easily perceived

(2) The larger size of the molecule slows its rate of diffusion and thus delays its absorption through the synovium.

The improved quality of delayed radiographs using Hexabrix in this trial suggests that these properties do

TABLE VI

DELAYED FILMS

	Conray	Hexabrix
(a) *Quality of meniscal coating*		
Excellent	0	4
Good	2	10
Acceptable	6	5
Poor	9	2
Total	17	21
(b) *Contrast imbibition*		
Absent	1	4
Slight	3	10
Moderate	13	7
Severe	0	0
Total	17	21

TABLE VIII

MISCELLANEOUS ADVERSE EFFECTS DESCRIBED BY PATIENTS FOLLOWING ARTHROGRAM

	Number (Conray + Hexabrix)
Sensations related to presence of gas in joint	22
Unstable	6
Difficulty bending knee	3
Bruising	2
Stiffness	1
'Faintness'	1
Rash on knee	1
Ache in thigh	1
'Hay-fever'	1

confer practical advantages. Systemic side-effects due to contrast media are very rare in knee arthrography because of the small volumes used and perhaps the intra-articular location, and Hexabrix has been shown to be tolerated better than conventional ionic media in vascular studies, but shows no demonstrable superiority in this investigation.

In this study, significantly more reports of pain in the knee were made immediately after the injection in the Hexabrix group than in the Conray group. It is known that sodium-containing salts tend to cause more pain than meglumine salts, though it seems unlikely that the low content of sodium in Hexabrix would have this effect, as the sodium concentration is lower than the physiological level of sodium in the synovial fluid. An alternative hypothesis is that the ioxaglate molecule itself may be more locally irritant to the synovium.

It is interesting to note that the patients reported more pain and discomfort on the questionnaire than they did to the radiologist at the time of the arthrogram. The same response was observed by Belli et al (1984) using the same protocol. This is probably a behavioural effect resulting from the method of inquiry, but could indicate that the discomfort only developed after the patients left the department.

The concentration of iodine in the two media used in the trial differs by 40 mg/ml. This was not corrected to standard concentration as this would not reflect accurately the way contrast media are used in the X-ray department. It seems probable that the effects of osmolality and viscosity could counterbalance each other and that the overall effect on the results would be small.

CONCLUSION

In this study Hexabrix has been shown to produce good photographic contrast as an arthrographic agent. Its theoretical property of maintaining a satisfactory arthrographic image on delayed films has been confirmed. Although its injection into the knee joint produces more discomfort to the patient than meglumine iothalamate, our experience over a considerable period of use does not lead us to believe this to be a serious objection and acceptance by the patient at the time is very satisfactory. At the present time, meglumine iothalamate injection 60% remains the standard inexpensive and satisfactory contrast medium of choice for knee arthrography. When and for whatever reason, usually in the presence of effusions or during acquisition of the technique, longer persistence of coating by the contrast medium in the joint is required, the use of Hexabrix is recommended.

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Radioaerosol assessment of mucociliary clearance: towards definition of a normal range

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ABSTRACT

Radioaerosol measurements of mucociliary clearance have been assessed in relationship to depth of particle penetration into the lung. The tests analysed were performed with 5 μm diameter $^{99}Tc^m$ particles inhaled under standardised conditions but at varying inhalation flow rates. Aerosol lung penetration was assessed by (i) penetration index (PI), a ratio of outer to inner zone radioactivity determined from a gamma camera image; and (ii) alveolar deposition (AD), a measure of activity retained at 24 hours and taken to represent deposition distal to the ciliated airways. Clearance rates in 30 tests on 19 normal non-smokers under the age of 50 varied significantly with aerosol inhalation flow rate, PI and AD. A normal range varying with PI is proposed although normal inter-subject variability remains high even after allowance for PI. Nevertheless 8 out of 12 patients with stable asthma and 21 out of 24 patients with chronic bronchitis demonstrated slow clearance lying outside the PI-based normal range

Mucociliary clearance is severely impaired in chronic obstructive airways disease (Camner, 1980; Pavia, 1984) Defective mucus transport may even play a pathogenic role in the development of such disease (Wanner, 1979; Mossberg, 1980; Yeates, 1982). Clearance from the whole bronchial tree can only effectively be assessed after inhalation of inert test particles in aerosol form which are then mechanically transported out of the lungs with the airways mucus. Even among normal individuals considerable variability of clearance rates is found (Camner, 1980, Yeates et al, 1982). Moreover, mucus transit through peripheral conducting airways is much slower than through the larger bronchi—so that differing patterns of aerosol deposition may influence the overall rate of clearance from the lung. Careful control of inhalation conditions cannot eliminate variability of deposition even among normal subjects (Stahlhofen et al, 1981). Airways obstruction tends to enhance deposition within the larger bronchi (Pavia et al, 1977) The overall extent of particle penetration into the lung may however be expressed in terms of a penetration index (PI), effectively defined as the ratio of outer to inner lung zone radioactivity from a gamma camera image (Agnew et al, 1981, 1984b).

Inhalation techniques intended to deposit particles over the whole bronchial tree inevitably also give some deposition distal to the conducting airways. Such alveolar deposition (AD) may be estimated from the fraction of particles retained in the lung 24 hours after inhalation—particle clearance from conducting airways sites being assumed complete by that time but clearance from the alveolar zone itself negligible. AD therefore distinguishes particles able to act as tracers of mucus transport from those deposited too distally to be transported with the conducting airways mucus.

In the present study, we investigated quantitatively the dependence of measured clearance rates in normal subjects on initial particle penetration into the bronchial tree. Although the calibre of the airways varies considerably from one person to another, the degree of penetration was found to depend mainly on the inhalation flow rate. We have therefore used flow rate itself, together with PI and AD, to characterise particle penetration. We also propose and discuss a 'normal range' for tracheobronchial retention expressed in relationship to PI. Data from patients with presumed mucociliary dysfunction are compared with this 'normal range.'

SUBJECTS AND METHODS

Radioaerosol deposition and clearance data from 30 tests on normal non-smoking volunteers aged under 50 were examined; 11 subjects had been tested twice (at differing inhalation flow rates), the other eight once only (Table I). Results were also available for comparison from 12 patients with stable asthma (Agnew et al, 1983, 1984a) and from 24 patients with chronic bronchitis (Table I). The asthmatic patients had been tested before and after a short course of oral corticosteroid therapy (2 weeks on 15 mg per day oral prednisolone followed by 2 weeks on 30 mg per day). Lung function was assessed 10 to 20 minutes before each radioaerosol test: forced expiratory volume in 1 s (FEV_1) by dry bellows spirometer (Vitalograph); maximal expiratory flow rate with 25% of forced vital capacity to be expired ($\dot{V}_{max}25$) from a flow-volume (air) curve obtained with a dry piston-cylinder spirometer (Ohio 840)

The radioaerosol technique used throughout (Pavia et al, 1980; Agnew et al, 1984b) involved inhalation of monodisperse 5 μm diameter unit density $^{99}Tc^m$-labelled polystyrene particles obtained from a spinning top

TABLE I

AGE, LUNG FUNCTION AND RADIOAEROSOL DEPOSITION DATA (MEAN ± SD)

	No. of subjects	No of tests	Age (years)	FEV_1 (% predicted)†	$\dot{V}_{max}25$ (% predicted)†	Radioaerosol inhalation flow rate (l min^{-1})	Penetration index (PI)	Alveolar deposition (AD) (%)
Normal subjects*	19 (9F, 10M)	30	29±10	111±31	85±32	32±13	0.63±0.14	55±13
Asthma	12 (4F, 8M)		43±13					
before steroids		12		69±20	22±9	26±4	0.37±0.11	23±6
after steroids		12		82±25	31±12	26±5	0.43±0.19	29±12
Chronic bronchitis	24 (2F, 22M)	24	66±7	43±18	9±4	39±10	0.40±0.15	28±12

*Mean ± SD values are calculated over all 30 tests, preliminary data from 6 subjects (2 tests each) have previously been reported (Agnew et al, 1981)

†Predicted values for FEV_1 are taken from Cotes (1979), for $\dot{V}_{max}25$ from Knudson et al (1976)

generator. Eight breaths of 450 ml volume were taken from approximately functional residual capacity Mean inspiratory flow rates were obtained from a pneumotachograph system connected to the aerosol tank. Each breath was followed by a pause of 3s during which breath was held to encourage particle deposition by gravitational sedimentation in the peripheral lung. After mouth-washing, gargling and a small drink of water, total lung radioactivity—typically about 1 MBq—was measured by means of twin (anterior-posterior) NaI (Tl) counters. This measurement was repeated at hourly intervals for 6 h and then again at 24 h. All measurements having been corrected for background and ^{99}Tc^{m} decay, the 24-h value (AD) was subtracted from the 0 to 6-h readings to convert these into readings of tracheobronchial retention.

Two gamma-camera images were obtained for all subjects (International General Electric large field-of-view camera). The first was of aerosol deposition (40 000 counts) recorded 10–20 minutes after inhalation and before any significant removal of particles from the lung field (Yeates et al, 1981). The second was of ^{81}Kr^{m} ventilation (200 000 counts) during tidal breathing. Both images were stored in a Varian V77-200/V77-600 computer system (Nodecrest Medical Systems) and subsequently aligned on the computer display with the aid of positional information from ^{57}Co marker sources worn at both image recording times. After correcting for background, PI (Agnew et al, 1981, 1984b) was calculated as the ratio of outer to inner zone ^{99}Tc^{m} activity divided by the same ratio for ^{81}Kr^{m}.

To assess clearance in the tests on normal subjects relative to inhalation flow rate, PI and AD, the 30 test results were, in each case, divided into two subgroups with, respectively, high and low values of the factor in question. Relationship of clearance to PI is expressed as a normal range, in terms of the 95% confidence limits of the regression of tracheobronchial retention (3 h after inhalation) on PI.

RESULTS

Factors affecting normal clearance

Table II summarises the characteristics of the subgroups into which the normal subjects were divided.

TABLE II

LUNG FUNCTION AND RADIOAEROSOL DATA FOR SUBGROUPS USED IN ASSESSING EFFECT ON CLEARANCE OF INHALATION FLOW RATE AND OF AEROSOL DEPOSITION PATTERN IN NORMAL SUBJECTS

Subgroup	FEV_1 (l)	$\dot{V}_{max}25$ (l s^{-1})	Inhalation flow rate (l min^{-1})	Penetration index (PI)	Alveolar deposition (AD) (%)
Low inhalation flow	4.1±0.9	2.4±0.9	21±4	0.72±0.11	62±10
High inhalation flow	4.1±0.7	2.3±0.6	42±9	0.54±0.12	48±12
High penetration index	4.0±0.7	2.4±0.8	27±12	0.74±0.08	65±7
Low penetration index	4.3±0.7	2.3±0.8	36±12	0.52±0.09	45±10
High alveolar deposition	4.2±0.8	2.6±0.8	26±12	0.73±0.10	66±6
Low alveolar deposition	4.0±0.7	2.2±0.8	37±11	0.53±0.11	44±8

Values shown are mean ± SD calculated over all 15 tests in each subgroup.
Mean age in each subgroup was 29 years (SD±10).

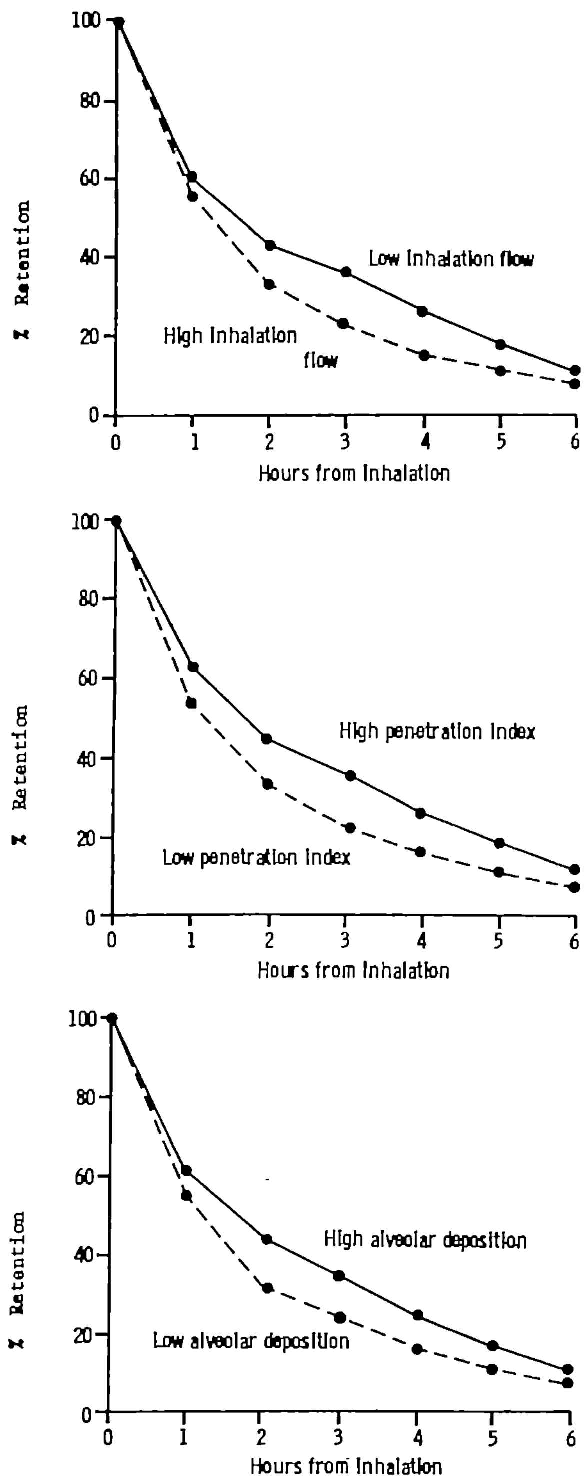

Fig 1

Effect of flow, PI and AD on tracheobronchial retention

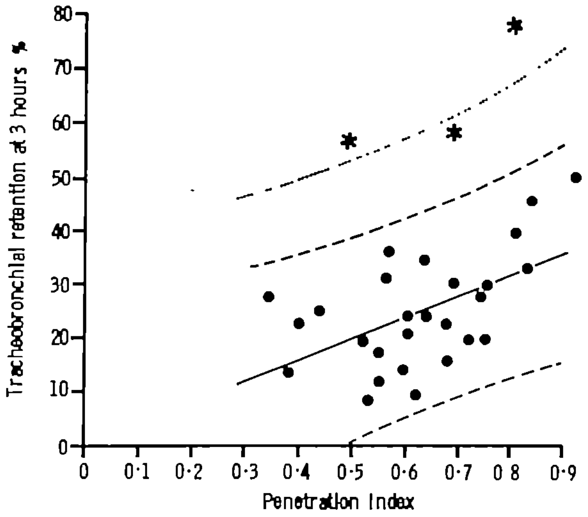

Fig 2

Relationship of tracheobronchial retention at 3 h to PI. Three 'outliers' are shown by asterisk symbols. Dashed lines indicate normal range (95% confidence limits) based on the 27 other tests. Dotted line indicates upper limit of normal obtained if 'outliers' are included in the calculation.

For each 'factor' (flow, PI or AD), the two subgroups simply comprise the 15 test results with the lowest values of the 'factor' in question and the 15 with the highest (no ties occurred to complicate this division). Figure 1 illustrates mean tracheobronchial retention for the three subgrouping pairs. In each case the paired retention difference is greatest 2–3 h after inhalation (3 h for flow and PI; 2 h for AD but with almost as well marked a separation at 3 h) and corresponds to 12–13% of initial tracheobronchial deposition.

A normal range for tracheobronchial retention at 3 hours

The analysis presented in Fig. 1 might mask clearance differences corresponding to very low or very high penetration. It is accordingly appropriate to compare retention with aerosol penetration over the full range of individual values recorded. This was done for retention at 3 h corresponding to the (approximate) time for maximum separation of the paired retention curves of Fig. 1. Visual inspection of the data suggested that three test results out of the 30 analysed demonstrated particularly slow clearance in relationship to particle penetration; this applied whether PI, AD or inhalation flow rate was used as an index to penetration. Retention in these three tests is shown by asterisk symbols in Fig. 2, which illustrates the relationship of 3-h tracheobronchial retention to PI The correlation between retention and PI calculated for all 30 tests is statistically significant ($r = 0.42$, $p < 0.05$) but more strongly so if the three 'outliers' are omitted from the calculation ($n = 27$, $r = 0.52$, $p < 0.01$); the regression

TABLE III

FREQUENCY OF ABNORMALLY INCREASED RETENTION RELATIVE TO 'NORMAL RANGE' BASED ON PENETRATION INDEX

	No. of test results	Abnormally high retention according to proposed normal range	Abnormally high retention according to more stringent normal range
Normal subjects	30	3	2
Asthma			
before steroids	12	8	8
after steroids	12	7	3
Chronic bronchitis	24	21	16

line shown in Fig. 2 is that calculated after omitting the three 'outliers'. The dashed lines indicate 95% confidence limits about that line for individual readings and define a 'normal range' for tracheobronchial retention at 3 h. Thus retention in a normal subject with as low a PI as 0.4 is expected not to exceed 36%. Retention in a normal subject with a relatively high PI of 0.8 should not (with 95% confidence) exceed 51%. The omission of the three 'outliers' has a considerable effect on these values: if recalculated with inclusion of the 'outliers' they would rise to respectively 50% and 68%, this more 'stringent' upper 95% confidence limit (based on all tests) being indicated by the dotted line in the figure.

Tracheobronchial retention at 3 h also showed a similarly strong linear correlation with inhalation flow rate ($n = 30$, $r = -0.42$, $p < 0.05$) and with AD ($n = 30$, $r = 0.46$, $p < 0.05$).

Both PI and AD were reduced in the patients with asthma and chronic bronchitis (Table III). Tracheobronchial retention at 3 h in these patients was compared with the normal range of Fig 2 (using a slight visual extrapolation of the range to low PI values for a few patients). As shown in Table III, the majority of the asthmatic and bronchitic patients had delayed clearance outside the normal range: two-thirds of them even outside the more stringent range (dotted line in Fig. 2) based on all 30 normal subject tests. After steroid treatment—which tended (Table I) slightly to increase aerosol lung penetration—five out of 12 asthmatic patients gave retention values which appeared normal in relationship to PI This would however rise to nine out of 12 if the higher normal limit line were to be adopted.

DISCUSSION

The mucociliary transport mechanism appears to work imperfectly in many clinical conditions (Camner, 1980). The ciliated epithelium may become damaged by infection, alterations of mucus properties may affect mucus–cilia coupling or the cilia themselves may malfunction due to ultrastructural abnormalities Radioaerosol tests have been used to monitor clearance changes brought about by a variety of drugs (Pavia, 1984) and of physiotherapy regimes (Rossman et al, 1982; Sutton, 1984). Yet—given the widespread use of such treatments—it would seem clinically (and economically) desirable to be able to establish, before treatment, whether a particular patient really has abnormally slow clearance requiring treatment. It might also be helpful to establish whether clearance after treatment reached a normal level

Our data from normal subjects (Fig. 1) imply that either PI or AD would serve equally well as a means of characterising aerosol deposition sites in relationship to their effect on the clearance curve. Inhalation flow rate too could serve equally well for normal subjects but would be inappropriate to apply to patients with airways obstruction in whom diminished airways calibre is likely to be the chief factor which reduces the penetration of particles to the lung periphery (Pavia et al, 1977). A particular advantage of PI is that it can readily be related to the concept of a mean clearance pathlength from deposition site to trachea. In particular a low PI implies that many particles are situated at sites relatively close to the trachea.

The form of 'normal range' we propose in Fig. 2 is obviously imperfect. The correctness of omitting three 'outliers' (all, to the best of our knowledge, healthy subjects with no clinical history of recurrent infections and with no indication of any factors that might predispose towards slow clearance) must be open to debate. To omit them from the normal range calculation implies—if really they are in fact 'normal'—acceptance of a 10% false positive rate in normal subjects. The corresponding false negative rate in chronic bronchitis—making the assumption that clearance should always be abnormal in chronic bronchitis—is 12.5%. The alternative normal range based on all 30 test results in normal subjects (Fig. 2) would still leave a false positive rate of 6.3% whilst increasing the false negative rate in chronic bronchitis to 33.3%.

The concept of PI, and the method we use of calculating it, are applicable to mucus clearance tests carried out with other sizes of aerosol particle or differing inhalation conditions. More extensive studies of what is meant by 'normal' tracheobronchial clearance should however ideally take account of irregularities of aerosol deposition rather than just of overall penetration.

Attention should also be paid to the possible effects of age: two previous studies have reported a tendency towards slower clearance in older subjects (Goodman et al, 1978; Puchelle et al, 1979) although a third has failed to detect any such effect (Yeates et al, 1982). Our present results quantitatively demonstrate the importance of the relationship between penetration of particles into the lung and their subsequent rate of clearance. The form of normal range we propose takes appropriate account of this and offers objective evidence as to how far, with existing techniques, it may be possible to characterise the clearance shown by a particular patient as either 'normal' or 'abnormal'

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Book reviews

1985 Year Book of Nuclear Medicine Ed by P. B. Hoffer, pp 424, 1985 (Blackwell Scientific, New York), £49 00.
ISBN 0–8151–4592–2

This book is best suited to intermittent reading, perhaps a bedside book, but if nuclear medicine lucubration is your choice it will cost you £49. It comprises over 300 selections from a wide variety of scientific, clinical and imaging journals published in the English language. These have been chosen by a team of editors from the United States, and are approximately one page summaries, some with illustration. Each is supplemented by an editorial comment which is in general cogent, but on occasion joky and irritating

The *Year Book of Nuclear Medicine* has now been published annually for nearly 20 years, and has provided enlightenment to those too busy to scan the clinical literature widely The necessity for such a book probably reflects the amount of redundancy in medical publishing today. However, a disadvantage is that the reader is dependent on the personal selection of the editors, which can be uneven. In this edition nuclear magnetic resonance comprises 17% of the papers, a questionable proportion for a book devoted to radioisotopes. The editors justify this by the "great diversity" of this particular publication, yet the primary value of a year book is provided by the concentration of material from a specialist field, rather than a wider coverage, interesting though this may be There are chapters on the common medical systems as well as physics, chemistry and radiation protection There is also a rather short preface reviewing tumour immunoscintigraphy.

A dip into this book can be rewarding, particularly if the abstract has derived from a journal not normally encountered by the average nuclear medicine practitioner

DUNCAN ACKERY

Diagnostic Imaging in Clinical Medicine, 3rd edn. By Rosalind H. Troupin, pp. xvi+210, 1985 (Year Book Medical Publishers, Chicago), £19.80.
ISBN 0–8151–8852–8

Small may be beautiful but just how concise can a textbook of diagnostic imaging be before some topics become over-simplified?

This manual had its origins in a series of handouts for medical students used with film reading sessions when the author was at the University of Washington. It is designed to be used in conjunction with film interpretation tutorials which are undoubtedly considerably more comprehensive than the teaching in radiology given to medical students here. Without such a course, the medical student may find himself seeking more information than this book provides.

However, it is a very stimulating introduction to radiology, alert to the needs of medical students, and is very readable It employs a problem-orientated approach and deals with those problems that one is constantly asked each week, not only by students, such as how best to exclude liver metastases or how to investigate a pulmonary nodule.

The format and emphasis in each chapter differs, but little attempt is made at systematic teaching For the chest, abdomen and bone films there is a "how to look at" section, but for more complex investigations the emphasis is on indications and choice of imaging method rather than image interpretation As somebody somewhere has to pay for each diagnostic investigation, a typical charge is given for each test The actual cost becomes a real eye-opener and reinforces the view expressed throughout the book that the reason for requesting an investigation should be "what for?" rather than "why not"

This book should be read by medical students starting their clinical training as an introduction to diagnostic imaging. If they can pass some of the ideas on to their clinical consultants, so much the better.

MARTIN L WASTIE

Nuclear Medicine Annual 1985. Ed. by L. M. Freeman and H. S. Weissmann, pp. x+352, 1985 (Raven Press, New York), $70.50
ISBN 0–88167–086–3

This, the latest edition of a well known annual, maintains the high standards set by the earlier editions and will enhance the high reputation obtained by them. The editors have clearly given each of the writers a precisely defined and well considered brief and all have been effectively executed. The field has been widened to include one paper on magnetic resonance imaging of the heart, and there is one on single photon emission tomography, a topic which, although it has been of interest for some years, is only now beginning to reveal its true clinical potential. No fewer than three of the 10 chapters are wholly or partly devoted to gastroenterological subjects, two covering gastrointestinal bleeding in adults and in children, respectively. There is, however, no significant overlap: a mark of effective editorial control.

Each section consists of a comprehensive, authoritative and clearly thought out survey of a subject in which there has been significant movement within the past couple of years. Indeed, this book is unusual in that, despite the specialised nature of a number of the chapters, there are no weak links. Certainly, anyone requiring an introduction to any of the topics covered could not do better than to read the appropriate section in this volume. Even those already working in the field are likely to obtain useful new insights. Although few will find every chapter of interest the quality is sufficient to justify purchase for only two or three. This volume should be available to anyone working in clinical nuclear medicine and can be strongly recommended.

M. V. MERRICK

1986, *The British Journal of Radiology*, 59, 153–156 FEBRUARY 1986

Assessment of priorities when introducing some radiation protection methods in radiodiagnosis

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(*Received March 1985 and in revised form August 1985*)

ABSTRACT

An estimate is made for the average population dose of ionising radiation for a diagnostic X-ray room, and indications are given of how the population dose can be assessed for individual rooms. By taking the percentage reduction of exposure on introducing selected methods of radiation protection, the expected population dose reduction is estimated for each method. Allowance is made for the length of use for a new method, and for loss of use for existing material. The population dose reduction is expressed in financial terms to obtain a ratio of this value to the cost of the protection method. Recommendations are made regarding the order of introduction of these methods.

Several techniques of radiation protection of the patient in X-ray diagnosis (which include the use of rare-earth screens, of carbon fibre material in table tops, cassette faces and grid covers, and of fibre interfaced grids) are highly cost-effective when spread over the life of apparatus (Russell, 1985). The problem addressed in this paper is how to determine the order in which these techniques should be introduced, if it is wished to carry out a programme of replacement of existing apparatus in the most efficient manner with regard to savings in cost and radiation.

METHOD

The annual population dose for each X-ray room is assessed. Hence the size of the annual reduction of population radiation exposure for each technique can be deduced, knowing the expected percentage dose reduction for each technique. This is then related to the cost of introducing the technique. The value of the radiation detriment reduction is assessed and the ratio of the value of the detriment reduction to the cost of applying the technique of dose reduction determined.

Annual room population dose

An actual count of the National Health Service diagnostic rooms in the North West Region of England gave 60 rooms/10^6 population. The addition of rooms outside the Health Service (private medicine, military and industrial) gives a total of 70/10^6 population. The workload in the non-NHS rooms tends to be less than in the NHS rooms.

The radiation exposure in the United Kingdom from diagnostic X-ray examinations is assessed at 250 μSv/head/year (Hughes & Roberts, 1984). This gives an average annual population dose for each room of 3.6 man-Sv. Most rooms are in the NHS and are fully used. Some will be more or less busy than average. Allowances should be made in the room dose assessment for the mix of examinations if this is thought to be different from average. If the workload of a room is known with respect to the number of specific examinations it may be possible to make an estimate of the room dose from the mean body dose (ICRP, 1982) for each examination and the number of examinations. It was found in the Manchester Royal Infirmary that the estimated room dose varied from 0.1 to 20 man-Sv, being highest in the vascular rooms and the barium screening rooms. A further indication of the workload of a room may be obtained from the number of examinations carried out in the room per year. There were estimated to be 393 000 radiological examinations/year/10^6 population in NHS hospitals in 1977 (Kendall et al, 1980). With 60 NHS rooms/10^6 population, each room, on average, should have a throughput of about 6500/year

It may be justified to weight the annual room dose, up or down. For instance, the radiation hazard is less for a room in a geriatric hospital because of the diminished genetic risk and because the elderly are less likely to live long enough to manifest a radiogenic tumour. Conversely, a room used for paediatric or obstetric work may have the estimated dose increased because of the greater genetically significant dose in these patients. The room dose is likely to be more if rare-earth screens are not used.

Expected dose reduction

The expected percentage dose reduction is assessed at 50% for rare-earth screens and 10% each for the other methods. Other values may be used if measurements indicate larger or smaller figures (Hufton & Russell, 1986)

Annual cost of the detriment

The National Radiological Protection Board (NRPB, 1983) suggest taking the cost of the harm to the population from ionising radiation as £2000/man-Sv for annual exposure of less than 50 μSv, £10 000 over the range 50–500 μSv and £50 000 in the 500–5000 μSv range. These are 1980 prices; inflation to 1985 is 42%. The radiation dose of the majority of single X-ray examinations falls into the middle band, but a significant number of examinations are in the top band, and a few above the top band. Multiple examinations of an individual within a year may push the dose up a band. It is, therefore, considered that the value of detriment for this exercise can be reasonably taken as £15 000/man-Sv.

The annual value of the detriment for each room is taken as £15 000 multiplied by the annual room dose in man-Sv. The annual value of the saving of the detriment is the percentage dose saving multiplied by the annual value of the detriment of a room.

Annual cost of application of methods of radiation protection

The cost of introducing each method is taken and this is divided by the number of years of expected use. More complicated methods of amortisation may be used if desired (ICRP, 1983). Screens and cassettes are assumed to have a 10-year life. Table tops and grids will have a life equal to the remaining life of the machine in which they are used: it is unlikely but not impossible that they will be re-used in a new machine. Carbon fibre grid facings and fibre-interspaced grids are considered together, as one is unlikely to be used without the other. Cassettes and screens are considered separately, but it may be difficult to remove old screens from cassettes and both cassettes and screen may have to be replaced together.

For cassettes and screens (as well as gridded cassettes) the cost is determined by the formula·

(10 − age of cassette or screen) × (current cost of old type of equipment).

The result is then added to the difference in cost between low-radiation cassette or screen and the older type, divided by 10. This is the value of the loss of use of the discarded cassette or screens plus the additional annual cost of the new one.

TABLE I

COST OF RADIATION SAVING FOR CARBON FIBRE MATERIAL GRID AND FIBRE GRID INTERFACE*

Years of use	Annual cost (£)	Cost of saving 1 man-Sv (£)	Ratio of detriment reduction to cost†
1	800	1100	14
2	400	560	27
3	260	360	42
4	200	280	54
5	160	220	68
6	133	190	81
7	114	160	95
8	100	140	108
9	88	120	123
10	80	110	135

*Assumed radiation reduction 20%. Annual room dose 3.6 man-Sv Annual radiation dose reduction 0.72 man-Sv Annual value of detriment reduction = £10 800. Unit cost £400; two grids/room, each 43 cm × 35 cm = £800.

†Note, two grids/room are assumed In many rooms only one grid will be needed, increasing the detriment cost ratio.

The cost of the carbon fibre material components is taken at present levels. With widespread use, their cost is likely to fall substantially.

Ratio of value of the detriment to the cost

The ratio of the annual value of the saving of the detriment to the annual cost is calculated. If this is greater than unity then the method of radiation protection is worth applying. If it is less than unity, it is not worth applying. The higher the ratio, the more cost-effective the technique. By comparing the ratios for the various methods, the most advantageous, with regard to the cost and the benefit can be found.

Note that if a single room is involved, the workload is likely to be irrelevant in assessing priorities If, for example, the workload is half the national average, all the ratios of the value of the saving of the detriment to the cost are halved; their relative position to each other remains the same. Only if the workload is very small is the throughput relevant: then it may be questioned if some of the less advantageous techniques are worthwhile.

Cost of saving 1 man-Sv

This has been calculated to compare with other methods of radiation protection, in particular outside medicine.

RESULTS

Tables I to IV give the results of these calculations. It is seen that all these methods of radiation protection are highly cost-effective, even if the apparatus has only 1 year's use, or if brand new cassettes or screens have to

TABLE II

COST OF RADIATION SAVING FOR CARBON FIBRE MATERIAL TABLE TOP*

Years of use	Annual cost (£)	Cost of saving 1 man-Sv (£)	Ratio of detriment reduction to cost
1	1000	2800	5.4
2	500	1400	11
3	330	920	16
4	250	690	22
5	200	560	27
6	170	470	32
7	140	390	39
8	130	350	42
9	110	310	49
10	100	280	54

*Assumed radiation reduction 10%. Annual room dose 3.6 man-Sv Annual radiation dose reduction 0.36 man-Sv Annual value of detriment reduction = £5400. Unit cost, £1000.

TABLE III

COST OF RADIATION SAVING FOR CARBON FIBRE MATERIAL FACED CASSETTES*

Age of cassettes to be discarded (years)	Value of discarded cassettes (£)	Annual cost (£)	Cost of saving 1 man-Sv (£)	Ratio of detriment reduction to cost
0	250	340	940	16
1	225	315	880	17
2	200	290	810	19
3	175	265	740	20
4	150	240	670	23
5	125	215	600	25
6	100	190	530	28
7	75	165	460	32
8	50	140	390	39
9	25	115	320	47
10	0	90	250	60

*Assumed radiation reduction = 10%. Annual room dose = 3.6 man-Sv Annual radiation dose reduction 0.36 man-Sv. Annual value of detriment reduction £5400. Unit extra cost £40–110, depending on size Eight cassettes/room – total extra cost £900, £90/year. Cost of eight old-type cassettes = £250

TABLE IV

COST OF RADIATION SAVINGS FOR RARE-EARTH SCREENS*

Age of screens to be discarded (years)	Value of discarded screens (£)	Annual cost (£)	Cost of saving 1 man-Sv (£)	Ratio of detriment reduction to cost
0	720	72	40	380
1	650	65	36	420
2	580	58	32	470
3	500	50	28	540
4	430	43	24	630
5	360	36	20	750
6	290	29	16	930
7	220	22	12	1200
8	140	14	8	1900
9	70	7	4	3100
10	0	0	0	Infinity

*Assumed radiation reduction = 50% Annual room dose = 3.6 man-Sv Annual radiation dose reduction = 1.8 man-Sv. Annual value of detriment reduction = £27 000. Unit extra cost – nil Eight screen pairs/room. Cost of average screen pair = £90, cost/room, £720.

be discarded to bring the new radiation protection efficient cassettes or screens into use. With more than one technique the percentage savings should be compounded If a different value of annual room population dose is taken, the values in the tables should be altered proportionally.

DISCUSSION

There is general agreement that ionising radiation causes harm, (ICRP, 1977; Committee on the Biological Effects of Ionising Radiations (BEIR), 1980, United Nations Scientific Committee on the Effects of Ionising Radiation (UNSCEAR), 1982). All of these authorities have agreed very similar levels of the magnitude of harm from a given dose (Russell, 1984). Over the comparatively small range of diagnostic exposure a linear dose–effect response can be assumed.

The cost-effectiveness of the methods of radiation considered above has already been shown (Russell, 1985). These results are presented to stress that even with a single year's use, the techniques are still cost-effective. Some techniques of dose reduction cost nothing; for instance, careful beam collimation. Of the techniques considered here, none can approach rare-earth screens in cost-effectiveness, and replacement of conventional tungstate screens should have priority in any programme The next most efficient method of protection is the use of grids interfaced with fibre and faced with carbon fibre material, but cassettes faced with carbon fibre material and carbon fibre material table tops may be more cost-effective, depending on the respective ages. For a room with a small population, radiation dose optimisation studies (ICRP, 1983) will help indicate the protection methods to apply In general, these studies will not be necessary if the ratio of detriment to cost is greater than 4.

One cannot hope that every room will be re-equipped overnight. It is hoped that finance will not be a problem, bearing in mind the cost-effectiveness of these techniques However, the manufacturers would not be able to provide the huge amount of material needed to update all radiological rooms in a short period. The figures in Tables I–IV enable a programme of replacement to be planned in a rational fashion. By considering the workload, age of apparatus, ages of patients and the relevant value of the ratio of detriment saved to cost, the most advantageous programme of renewal can be planned for a department.

For too long, radiation protection of the patient in radiodiagnosis has been underfunded. In the United Kingdom the Department of Health and Social Security (DHSS, 1981) have indicated that methods of health promotion should be financially encouraged. Surely radiation protection in this cost-effective context is a method of health promotion worthy of support? Far larger sums are spent outside medicine on radiation protection than those found here. The figures in the tables of the cost of saving 1 man-Sv may be compared with values of £5000 to £3.3 × 10^6 spent to save the same amount of radiation exposure in nuclear power generation (Russell & Webb, 1985).

There is no doubt that, in general, the hazard of exposure to diagnostic X rays is far less than the hazard of not having an examination (Adrian, 1960), but a sizeable detriment does exist from radiodiagnosis and this should be reduced by methods of protection which do not reduce the quality of the examination and which are cost-effective.

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Correction

Serial qualitative maternal nephrosonography in pregnancy. By K. A. Cietak and J. R. Newton. *British Journal of Radiology* (1985), *58*, 399–404.

Serial quantitative maternal nephrosonography in pregnancy. By K. A. Cietak and J. R. Newton. *British Journal of Radiology* (1985), *58*, 405–413.

The authors have asked that Mr P. Davis, Lecturer in Statistics at the University of Birmingham, be included in the list of authors for the above papers. They apologise for this omission.

1986, *The British Journal of Radiology*, *59*, 157–163 FEBRUARY 1986

The use of carbon fibre material in table tops, cassette fronts and grid covers: magnitude of possible dose reduction

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ABSTRACT

The X-ray transmission of a number of radiographic components, some of conventional construction and some incorporating carbon fibre material, has been measured under clinically realistic conditions. At 80 kVp the use of carbon fibre materials enables the patient dose to be reduced by 30–50% depending on the existing equipment, type of examination and technique used. Typically the dose can be reduced by 3–15% by changing the table top, 6–12% by changing the front of the film cassette and 20–30% by using a grid with carbon fibre covers and fibre interspace. The higher cost of carbon fibre components can normally be justified by such dose savings. An indication of the absorption of all such components should be provided by manufacturers.

Carbon fibre composites for radiological applications are made from pure carbon fibres woven into a fabric and bound with a resin. They combine the properties of high strength and stiffness with low X-ray absorption; carbon fibre material can be as strong as aluminium for only half the weight and about one eighth of the absorption (Richter, 1981).

The use of carbon fibre material has been suggested for many applications in the primary beam of diagnostic X rays. These are.

(1) table tops,
(2) cassette fronts,
(3) grid covers,
(4) automatic exposure control devices,
(5) image intensifier faces,
(6) compression plates for film changers, and
(7) compression cones and faces, particularly in mammography.

A further possible use, apparently not yet commercially available, would be to replace the grid interspace material—which is currently aluminium, plastic or paper fibre—with carbon fibre.

However, carbon fibre is not widely used in diagnostic radiology, except for some specialised applications such as compression plates for angiographic film changers, and table tops for computed tomography and angiography, where strength and good flexural properties are demanded. The reason for this has probably been the relatively high cost in the past, although this has continued to fall over recent years (Richter, 1981). No disadvantages have been reported with regard to wear, fatigue fracturing, fraying, health hazard or fire risk.

Many of the reports on the patient dose reduction which results from the use of carbon fibre materials are of limited value, either because they were not obtained under clinically realistic conditions, or the test conditions were not adequately specified. Reports which do satisfy reasonable criteria indicate wide variations in the expected dose reductions. There are several reasons for this. Firstly, the carbon fibre components have differed, often being prototype or experimental samples. Secondly, conventional commercial table tops and cassettes vary considerably in their attenuation due to the use of different materials and different thicknesses. Lastly, the attenuation of conventional materials can be quite markedly energy dependent, especially at low energies, and so the expected reduction in dose is affected by various factors, such as kilovoltage, thickness and composition of test phantom or patient, and properties of antiscatter grid.

For a realistic appraisal of the effects on patient dose it is necessary to make measurements under clinically realistic conditions using the same type of conventional components currently in use and the same type of carbon fibre components which would be used to replace them.

METHOD

The experimental arrangement used is shown in Fig. 1. A hardboard phantom of dimensions 30 cm × 30 cm × 19.5 cm was used to simulate a patient. The depth of 19.5 cm was equivalent, in terms of attenuation, to 17.6 cm of water. The distance from the focal spot of the X-ray tube to the rear face of the phantom was fixed at 90 cm and the beam size adjusted to give a field size of 30 cm × 30 cm at a distance of 1 m from the focus. Samples of table top were positioned immediately behind the phantom, followed by the antiscatter grid at a distance of 5 cm behind the phantom, and the front of the screen-film cassette at a further distance of 3 cm behind the grid. The geometry is thus typical of that used in clinical radiography.

Radiographic exposures were produced by a Philips generator and X-ray tube giving a 3-phase 6-pulse voltage waveform. The kVp was checked with a

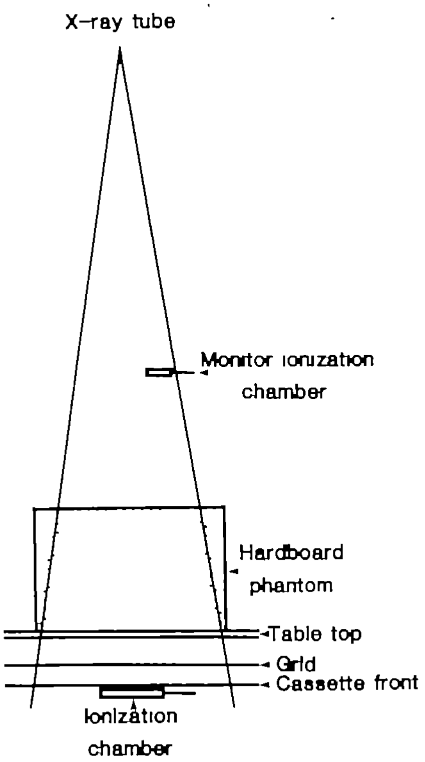

FIG. 1

Experimental arrangement for measuring X-ray transmission of components.

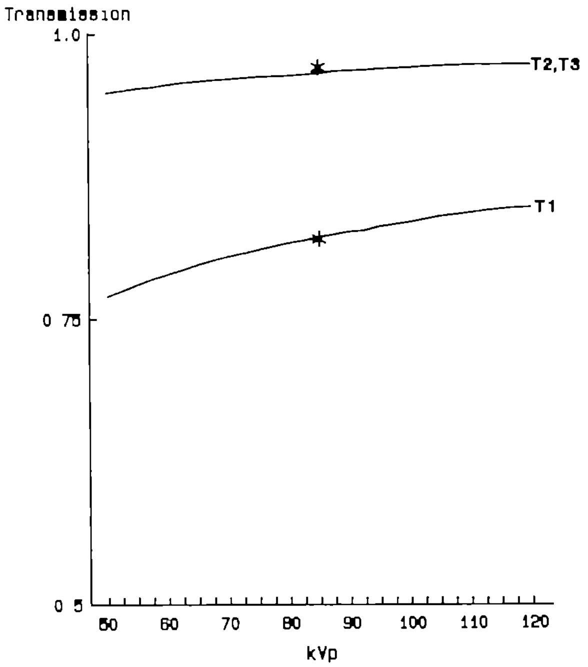

FIG 2

Table top transmission as a function of kVp. See Table I for key to symbols (* result using ^{241}Am).

Keithley 35080 kVp divider and was within 1 kV of the set value at all settings used.

The transmitted radiation was measured with a Victoreen 660-5 ionisation chamber, positioned as shown in Fig. 1, and a Victoreen 660-1 readout unit. The transmission of the particular component under test was thus given by the ratio of this reading to that of a second reading made with the item removed from the beam. In both measurements any variations in X-ray tube output were monitored and corrected for by using a second ionisation chamber between the tube and phantom.

Measurements were made at 10 kV intervals from 50 kVp to 120 kVp and some of the measurements were repeated with phantom thicknesses of 29.4 cm and

TABLE I

RADIOGRAPHIC COMPONENTS TESTED

Table tops			
T1	Wareite	7.9 mm thick	
T2	Carbon fibre	10.6 mm thick	
T3	Carbon fibre	13 3 mm thick	
Grids			
G1	Al cover/Al interspace	Liebel Flarsheim	Micralum 10:1 34 lines cm^{-1}
G2	Al cover/Al interspace	Liebel Flarsheim	Ultralum 10:1 40 lines cm^{-1}
G3	Al cover/Al interspace	Philips	10·1 24 lines cm^{-1}
G4	Al cover/Al interspace	Philips	8·1 40 lines cm^{-1}
G5	Carbon fibre cover/fibre interspace	Smit Rontgen	8·1 44 lines cm^{-1}
Cassettes			
C1	Al front	Kodak X-Omatic	
C2	Mg alloy front	GEC Watson	
C3	Carbon fibre front	Rego	

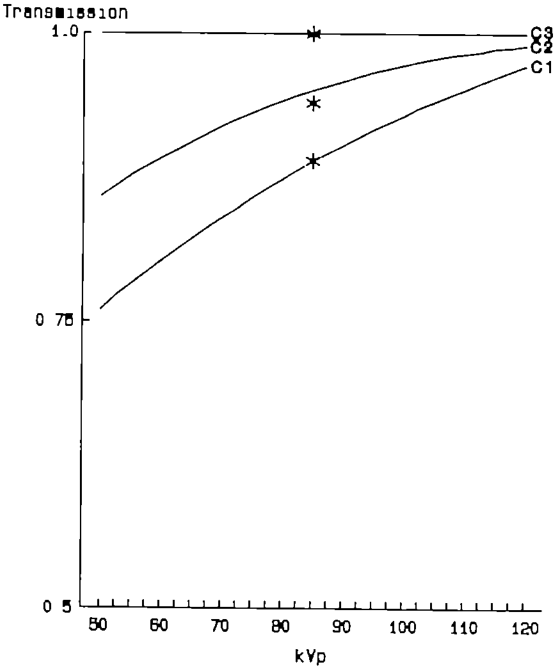

FIG 3

Cassette front transmission as a function of kVp. See Table I for key to symbols (*result using ^{241}Am)

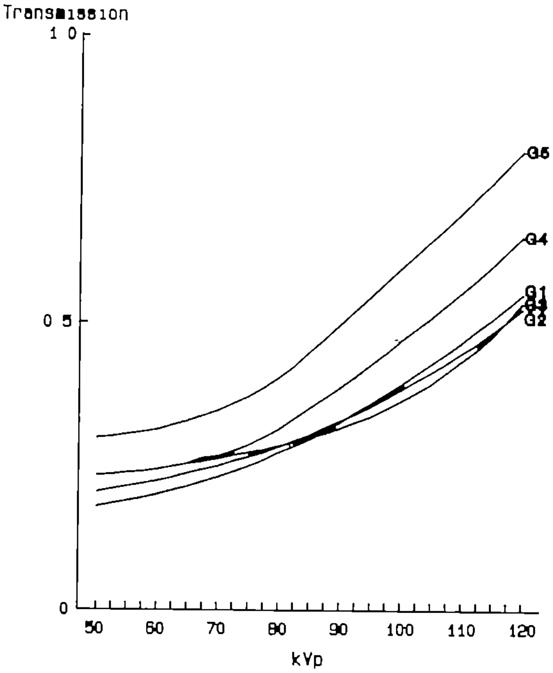

FIG 4.

Grid transmission as a function of kVp. See Table I for key to symbols.

9.9 cm, equivalent to 26.5 cm and 8.9 cm of water, respectively.

The various radiographic components tested are listed in Table I. When the transmission of the different table tops were, being measured, grid G2 and cassette C1 were in position; for the grids, table top T2 and cassette C1 were used; for the cassettes, table top T2 and grid G1 were used. Time did not permit measurements to be made with all possible combinations of table top, grid and cassette, but it was possible to calculate transmissions for unmeasured combinations as long as one assumed that the beam hardening produced by the different components did not differ significantly Tests showed that this was a valid assumption. Both samples of carbon fibre table top were provided by Fothergill Rotorway Composites Ltd, the thinner one having been in use as a section of a table top constructed for investigations into scanning slit radiography. All of the other components were representative of commercially available products.

The transmission of a number of other table tops was measured *in situ* using an 18.5 GBq (500 mCi) ^{241}Am source and scintillation detector. The shielded source holder and shutter assembly was similar to that described by Hewitt (1982). A Nuclear Enterprises GP7 scintillation probe connected to a PCM5 ratemeter was used to measure the count rate from the source, and the measurements were performed with a source–detector separation of 50 cm, a 1 mm-thick lead attenuator being

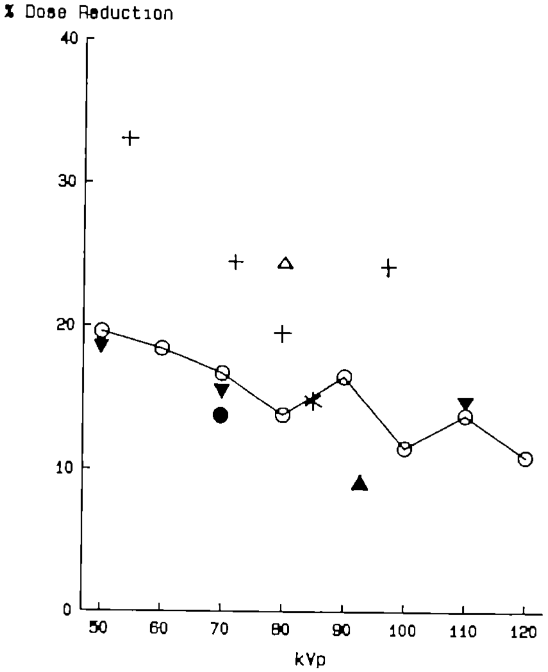

FIG 5

Dose reduction achieved by replacing conventional table tops with carbon fibre table tops (○ this work, * this work ^{241}Am, ● DHSS (1981), ▲ Ingles (1979), △ Trefler (1979), ▼ Haus et al (1980), + Eberhardt (1978)).

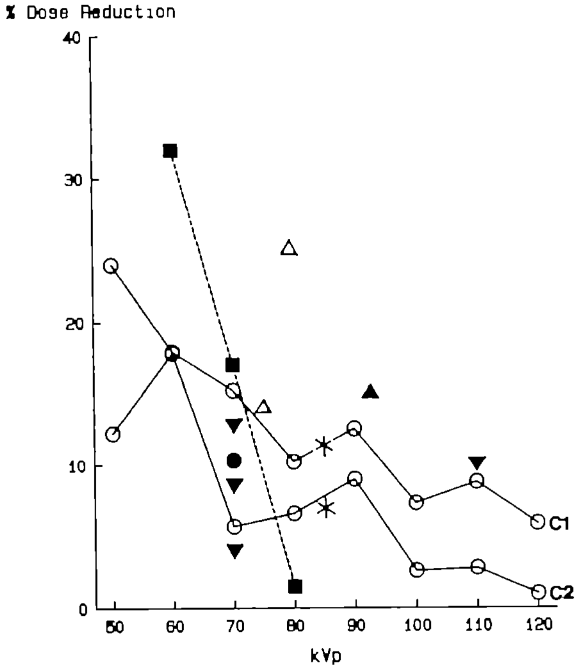

FIG 6

Dose reduction achieved by replacing conventional cassette fronts with carbon fibre cassette fronts (○ this work, * this work ^{241}Am, ● DHSS (1981), ▲ Ingles (1979), △ Trefler (1979), ■ Trefler (1980), ▼ Haus et al (1980)).

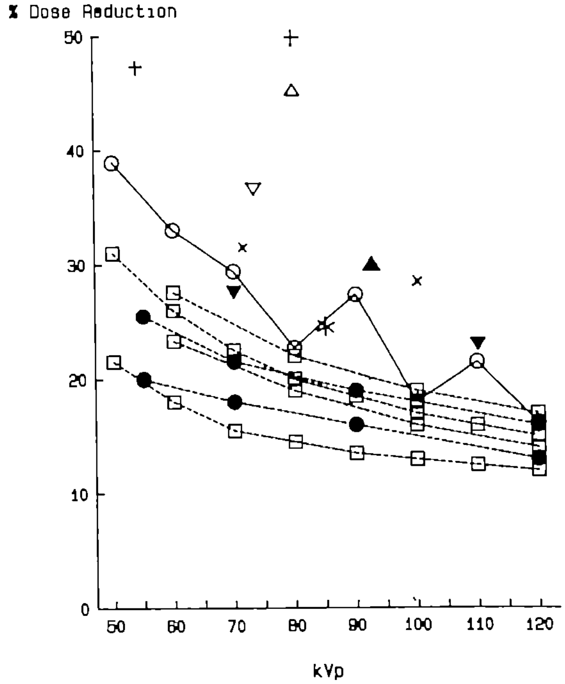

FIG. 7.

Combined result of replacing conventional table tops and cassette fronts with carbon fibre components (○ this work, * this work ^{241}Am, ● DHSS (1981), ▲ Ingles (1979), △ Trefler (1979), □ Shuping et al (1980), ▼ Haus et al (1980), ▽ SRE (1979), × Buden (1979), + Eberhardt (1978))

used to reduce the count rate to approximately 3000 cps. A transmission measurement was then made by inserting the component under test between the source and detector. As long as the component was not placed close to the detector, its position was found not to be critical. For consistency it was always placed close to the source. Since this was such a quick and easy measurement to make it was repeated on all the components tested and the results compared with those obtained under the more realistic conditions already described.

RESULTS

The measured transmissions for the different table tops and cassette fronts, as a function of kVp, with the 19.5 cm-thick phantom, are shown in Figs 2 and 3, respectively. As can be seen from Fig. 2, in terms of X-ray transmission it was not possible to distinguish between the two carbon fibre table tops of different thicknesses. Also shown in these figures are the transmissions measured at 59.5 keV using the americium source. It can be seen that these correspond closely to the measurements made at 85 kVp with the X-ray set. Measurements using the americium source on a further seven conventional table tops from three different manufacturers gave transmission values ranging from 0.87 to 0.94. Transmission data for the grids are shown in Fig. 4. This does not, of course, indicate the true effect of the different materials used in the construction of the grids since the transmissions will also be greatly influenced by their scatter rejection properties.

These data have been reinterpreted in terms of possible dose reductions to enable comparisons to be made with other publications on the subject. The results are shown in Figs 5 to 8. The only data included in these figures are those obtained under clinically realistic conditions, the criteria for which were that the tests had been performed with normal diagnostic X-ray sets, using a patient or patient phantom, table top, antiscatter grid and cassette in a similar manner to normal radiographic practice.

Figure 9 shows the overall dose reduction which may be obtained by exchanging all three items, namely table top, grid and cassette, with ones containing carbon fibre material.

Also shown, in Fig. 10, is the effect of using phantom thicknesses of 29.4 cm and 9.9 cm, in addition to 19.5 cm. The reason for the poorer dose advantage with the thinnest phantom is not obvious, but is probably due to the smaller quantities of lower energy scatter compared with the thicker phantoms. This would

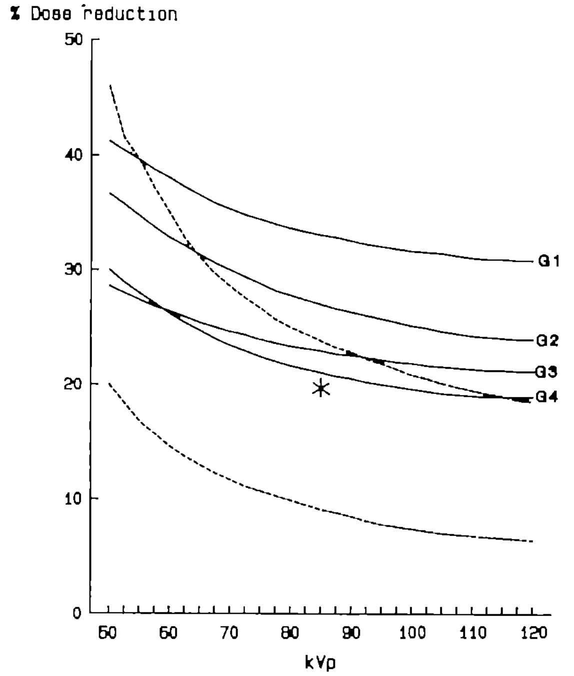

FIG 8

Dose reduction achieved by using carbon fibre grid covers (— this work, * this work ^{241}Am (G4) (see Table I for key to symbols), --- Richter, 1981, upper curve for conventional grid with Al interspace and Al covers, lower curve for conventional grid with fibre interspace and Al covers).

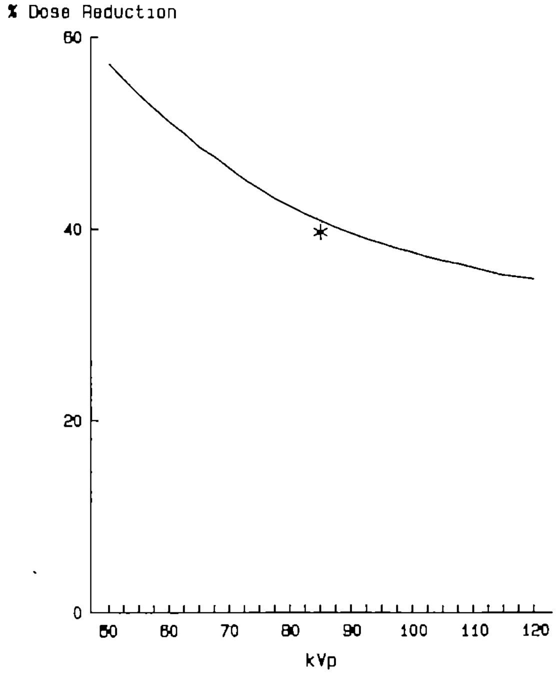

FIG. 9.

Overall dose reduction resulting from the use of carbon fibre materials in table tops, grid covers and cassette fronts (* indicates result using ^{241}Am).

appear to outweigh the lower mean primary-beam energy which results from the lower filtration of the thin phantom. More work is needed to quantify this effect.

DISCUSSION

Figures 5 to 9 show the expected dose reduction resulting from the use of carbon fibre components. Despite minimising beam quality differences by including only those data obtained under similar, realistic conditions, the reductions vary considerably due to differences in the transmission of both the conventional and carbon fibre material components tested. The conventional grids available for testing all had aluminium interspace material as well as aluminium covers, whereas the carbon fibre grid not only had carbon fibre covers but also a 'fibre' (presumably paper-based) interspace. Although grids with fibre interspaces are generally available, most X-ray equipment is supplied with aluminium interspaced grids. However, Richter (1981) was able to compare an aluminium cover/fibre interspace grid with a carbon fibre cover/fibre interspace grid and in this case the dose reduction is obviously much less, as can be seen from Fig. 8.

In this study, grids of identical construction, in terms of grid ratio, strip density and lead content, differing only in the materials used for the covers and interspace, were not available for test. This will clearly affect the magnitude of any possible dose reduction However, commonly used grids were included in the tests and these gave results, except perhaps at the lowest energies, similar to those reported by Richter (1981), who was able to test grids of identical scatter rejection properties.

In summary, the data obtained in this study show that the use of carbon fibre table tops and cassette fronts can reduce the patient dose by about 3–15% and 6–12%, respectively, while grids with carbon fibre covers and fibre interspace can give a further 20–30%

TABLE II

COMPARATIVE COST OF CONVENTIONAL AND CARBON FIBRE CASSETTES

Size (cm)	Cost of cassette in £, UK prices, July 1984	
	Aluminium front	Carbon fibre front
15 × 30	35	77
18 × 24	33	74
24 × 30	38	105
35 × 35	46	152
35 × 43	50	163

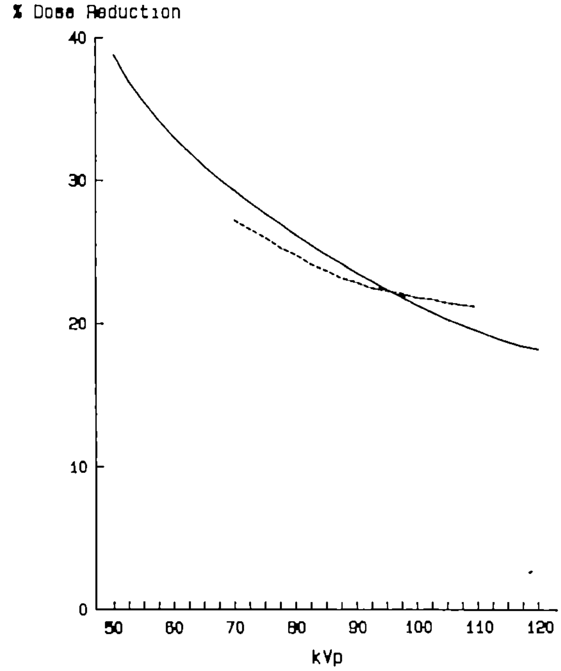

FIG. 10

Effect of different phantom thicknesses on dose reduction achieved with carbon fibre table tops and cassette fronts (— 19.5 cm phantom, --- 29.4 cm phantom, · · 9.9 cm phantom)

reduction. Thus the overall dose reduction can be expected to be in the range of 30–50%. Although the sample table top tested (T1) gave a dose reduction at the top end of the range quoted above, the americium tests showed that some table tops in common use gave rather higher transmissions, hence the lower figure of 3% for the dose reduction The figures quoted above refer to an X-ray tube potential of about 80 kVp As expected the potential dose reduction is greater at low energies, but it is nevertheless significant over the whole diagnostic energy range.

It is interesting to note that the figures obtained with the americium source agree quite well with those using the X-ray set at about 85 kVp. This suggests that such a method, which is both quick and easy, could be used by manufacturers to supply transmission information of their radiographic components to the user This should always be provided

The use of carbon fibre materials may alter the image contrast It may be reduced by increased transmission of scatter through carbon fibre or it may be increased due to less scatter from the carbon fibre components themselves and additional transmission of the lower energy component of the primary beam. Different investigators have shown a decrease in contrast in certain circumstances (Trefler, 1980), an increase (Richter, 1981; Poznanski & Pavelec, 1983) or no alteration (DHSS, 1981).

In the past the high cost of carbon fibre material has been a severe disadvantage, but the price of these components has fallen rapidly. The additional cost of a flat carbon fibre material table top over conventional material is about £800, so the additional cost over the lifetime of a table is very small. Sample prices for cassettes with conventional fronts and with carbon fibre fronts are given in Table II. Typical UK prices for aluminium interspaced grids are, for size 24 cm × 30 cm, £120, and for 35 cm × 43 cm, £230. The prices for fibre interspaced grids of these sizes are £223 and £319, respectively: about £100 extra. Current UK prices for grids made with covers from carbon fibre material are an extra £33 for sizes up to 24 cm × 30 cm, £55 up to 35 cm × 43 cm and £86 for size 35 cm × 43 cm The demand for carbon fibre material components is, at present, minute. Their prices should fall substantially as demand increases. Although the details will vary according to local circumstances, the extra cost of carbon fibre components is far outweighed by the value of the consequent reduction in patient dose (Russell, 1985)

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Book review

The Principles and Practice of Ultrasonography in Obstetrics and Gynaecology, 3rd edit Ed. by Roger C. Sanders and A Everette James, pp. xvi + 646, 1985 (Appleton-Century-Crofts, Norwalk, Connecticut), £86.25

ISBN 0–8385–7956–6

This is the very much expanded and welcome third edition of a well known textbook of obstetric and gynaecological ultrasound. In the preface the editors describe this book as a reference text, but also one that can be read in its entirety On both counts these claims appear well met for the most part.

Despite 43 chapters and nearly twice as many authors, the overall standard of content is extremely high The book is copiously illustrated with many high-quality scan images together with simple line drawings, graphs and tables where appropriate.

In the obstetric sections the chapters on the prenatal diagnosis of fetal abnormality are particularly pleasing, with contributions from several well respected British authors The newer techniques such as Doppler studies of fetal blood flow and interventional procedures are well described. Unfortunately, however, the rapid progress in these fields means that these sections are already somewhat outdated at the time of publication. A small criticism must be levelled at the over-succinct section on fetal echocardiography in that there is little description of the structural cardiac abnormalities that might reasonably be diagnosed pre-natally The reader would have to refer elsewhere for this information

The gynaecology section covers the subject thoroughly and includes honest discussion of the many pitfalls to which the unwary may fall prey in the diagnosis of pelvic pathology.

In conclusion it must be said that this volume provides the "gold standard" reference text in this subject It is to be recommended as a bench book for any department trying to provide an up-to-date service in obstetric and gynaecological ultrasound

HEATHER ANDREWS

Book reviews

Computed Tomography of the Head and Neck, Contemporary Issues in Computed Tomography, Vol 5 Ed by Barbara L. Carter, pp. x+341, 1985 (Churchill Livingstone, New York), £45 00.

ISBN 0–443–08380–0

One has only to count the pages in *Index Medicus* that are required to list the publications on computed tomography in any one year to realise the vast amount of literature that is published on this subject Seeking information quickly on some aspects of computed tomography can be quite a daunting task and the "Contemporary Issues in Computed Tomography" series can be of value This, the latest in the series, consists of 11 chapters written by well known authors and devoted to problem areas of the neck, temporal bones, paranasal sinuses, orbit, base of tongue and salivary glands.

The first 10 chapters have a standard format considering the radiographic technique followed by the basic anatomy and the computed tomographic anatomy, before proceeding to pathological appearances. The text is concise but very readable and contains an adequate number of references to guide the reader in widening his knowledge, but very few references later than 1982 are quoted. The standard of illustration is high and the chapters on the orbit and the temporal bone are worthy of special merit although an illustration of an intraorbital neurofibroma is not to be found. Illustrations of other enhancing lesions about the petrous apex, such as meningioma and ectatic basilar artery, would also have been valuable inclusions in the section on the temporal bone.

The final chapter is devoted to a comparison of magnetic resonance imaging of the head and neck with the accepted "gold-standard" of computed tomography. The fact that "two techniques are at very different stages in their development" is clearly seen in the quality in some of the MR images reproduced in this chapter. However, in 10 years time the situation may well be rectified by a future volume of this series devoted to MR of the head and neck.

To round off the book there are three short case discussions which are each accompanied by a few key references and some very good but rather small illustrations The work is to be recommended as a quick reference book in any department involved in computed tomography and is valuable reading for trainees in diagnostic radiology and for otolaryngologists who wish to get an overall picture of computed tomography in the head and neck

J. V. OCCLESHAW

Computed Tomography of the Pelvis, Contemporary Issues in Computed Tomography, Vol. 6. Ed by James W. Walsh, pp. 267, 1985 (Churchill Livingstone, New York), £42 50.

ISBN 0–443–08386–X

Many radiologists will remember the considerable difficulties encountered when interpreting anatomy and pathology on the early pelvic CT images. With more experience and improved scanner technology, the situation has improved. Over the past 4–5 years there has been an increasing number of papers, the majority from North America, reporting experience with CT imaging of the pelvis. This book, sixth in the series "Contemporary Issues in Computed Tomography", is essentially a review of that experience

Nine chapters cover a variety of subjects, commencing with an excellent account of the normal anatomy and technique, followed by detailed consideration of various pathological processes, from pelvic fractures and skeletal tumours to staging of pelvic visceral malignancy There are also individual chapters on pelvic abscesses and the paediatric pelvis The role of CT and, wherever appropriate, the place of other imaging techniques are outlined in each chapter.

Some 25% of the book is allocated to the musculo-skeletal system: the account on pelvic and acetabular fractures is good and well illustrated, but the skeletal tumours receive an exhaustive treatment with inclusion of superfluous detail more suitable for a general text on skeletal radiology. The chapter on staging of bladder and prostate cancer is worthy of mention: it is lucid, authoritative and well balanced, providing a succinct description of the difficulties of interpretation, limitations and advantages of CT. Elsewhere , importance is given to the role of contrast enhancement in the staging of cancer of the cervix and uterine body, the need for further study of early-stage cancers, where CT has a high false positive and false negative rate, is acknowledged. The importance of CT in the detection of recurrent rectal tumours is outlined in a separate chapter on recurrent malignancy. There is, however, no mention of the role of CT in the pre-treatment evaluation of colo-rectal tumours

In summary, this book is a good review of pelvic computed tomography and the illustrations are of exceptionally good quality. It will be a useful addition to any department involved in whole-body CT scanning

H. MAMTORA

1986, *The British Journal of Radiology*, 59, 165–170 FEBRUARY 1986

The risk of diagnostic radiation of the newborn

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(*Received March 1985 and in revised form June 1985*)

ABSTRACT

The amount of diagnostic radiation received by neonates at a large maternity hospital in 1982 was calculated. The risk of inducing neoplasia is unlikely to be greater than one in 280 000 for each radiograph of chest or abdomen. Provided that the exposure of the newborn to radiation at the John Radcliffe Hospital is typical of the rest of the country, and excluding cardiac catheterisation and computed tomography, we estimate that at most one to two cases of malignant disease per year may be caused by diagnostic radiation in the United Kingdom. Genetic risks appear to be negligible. The risks of not using radiography in newborn patients outweigh the risks of inducing malignant or genetic disease.

Carmichael and Berry (1976) pointed out that small or sick newborn infants may have considerable numbers of radiographs taken and that indications for radiography in this group of patients should be carefully considered because of the possibility of inducing subsequent malignancy (Bithell & Stewart, 1975). The present study was undertaken to find out how many radiographs of babies were being taken in a large maternity hospital and to assess the risks involved in these investigations.

METHODS

The radiographs of all babies born in 1982 in the John Radcliffe Hospital were examined to assess the part of the baby included on the film, and the radiation dose received by the babies was calculated.

The radiographs of babies born in 1982 and radiographed in 1983 were included; but those babies born before January 1, 1982 and radiographed in 1982 were not included.

The radiographs of babies transferred to other hospitals were also traced and information on these is included in the results given below. All babies born in 1982 who were radiographed between birth and final discharge from hospital as inpatients were included whatever their age.

The radiographs found in the radiograph packets or recorded in the radiographic files form the basis of this survey. However, an allowance for radiographs taken but discarded as unsatisfactory should be made. Berry and Oliver (1976) carried out a survey of discarded radiographs and concluded that this amounted to approximately 5% of all radiographs taken. In order to allow for this additional source of radiation 5% has been added to the estimated radiation dose received during radiography.

Records of screening, cardiac catheterisation and computed tomography were also obtained and are discussed below.

Calculation of radiation dose

The radiation doses were measured in air at 100 cm from the X-ray focus using a Pitman 37c dosemeter and 35cc ionisation chamber. Three readings at each kV and mAs setting were made and the results averaged. The readings agreed to within 10%. The skin doses were then calculated, appropriate corrections being made for the focus-to-skin distance and backscatter. The radiographs were taken with a Picker Portable Capacitor Discharge Unit with an Hitachi X-ray tube having a total (inherent + added) aluminium filtration of 4.5 mm. Kodak Ortho G films between Kodak regular screens were used. The exposure factors quoted were for babies weighing 2.5 kg.

An estimation of the dose attributable to fluoroscopy was also made. The results are summarised in Table I. The average dose per exposure for an examination of chest or abdomen, 0.07 mGy, is similar to that given by Wesenberg et al (1977).

RESULTS

During 1982 there were 5543 births of whom 18 were still-births. Four hundred and thirty babies (7.8% of live births) born in the hospital were admitted to the Special Care Baby Unit (SCBU). In addition 71 babies were admitted who were born outside the hospital; these have been excluded from the study. Thirty-eight mothers were admitted to the John Radcliffe Maternity Hospital from hospitals outside the district because of obstetric problems. Two babies were still-born and 37

TABLE I

RADIATION DOSES MEASURED DURING RADIOGRAPHY

Examination	X-ray exposure	Skin dose/exposure
Premature babies (chest + abdomen)	50 kV 4 mAs 100 cm focus-film distance	0 07 mGy
Skull (babies)	60 kV 6 mAs	0 12 mGy
Fluoroscopy	45 kV 0 5 mA	1.3 mGy/min

TABLE II

NUMBER OF RADIOGRAPHS TAKEN OF EACH BABY IN THE JOHN RADCLIFFE MATERNITY HOSPITAL IN 1982

No. of radiographs per baby	No. of babies	Deaths	No of radiographs
1	155	4	155
2	50	0	100
3	32	2	96
4	20	5	80
5	13	1	65
6	8	1	48
7	10	0	70
8	8	0	64
9	9	1	81
10–14	8	0	88
15–19	6	2	107
20–24	13	2	274
Over 25	18	1	1059
Total	350	19	2287

babies born to these mothers were admitted to the SCBU. These babies and mothers have also been excluded from the study.

Radiography and fluoroscopy

Of the 5488 live babies whose mothers were delivered at the hospital (excluding mothers admitted from outside the district) 252 were radiographed in the SCBU and 98 from the lying-in wards. Thus 6.4% of babies were radiographed. A total of 2287 radiographs were recorded for these 350 babies, 1547 AP chest, 159 lateral chest, 363 chest and abdomen, 105 abdomen, 24 skull and 89 other radiographs. The number of radiographs taken of each baby is shown in Table II. Six of these 350 babies in the Special Care Baby Unit were fluoroscoped (2 contrast enemas and 2 contrast swallows and meals, 1 myelogram and 1 screening diaphragm). Fluoroscopy was recorded on videotape with fluoroscopy times varying from 3 min 30 s to 10 min 50 s with an average of 5 min 50 s.

The radiation received by the 350 babies radiographed and fluoroscoped was calculated using the dose estimates given in Table I together with the number of radiographs taken as given in Table II. The resulting estimate of total radiation exposure for this group of babies, making an approximate allowance for spoilt radiographs, is given in Table III. These figures exclude radiation exposures during cardiac catheterisation and computed tomography, which are discussed separately below.

Radiography during cardiac catheterisation

Six babies had cardiac catheterisation before leaving the hospital; three of these babies died. The total skin dose received by the six babies was 787 mGy, the individual doses varying from 52 mGy to 210 mGy with an average of 131 mGy.

TABLE III

SOURCES OF RADIATION

	mGy
Radiography in the John Radcliffe Hospital	161.3
Radiography in other hospitals	1.8
5% addition for spoilt film	8.2
Fluoroscopy	49.0
Total	220.3

Radiation from computed tomography

Computed tomography (CT) of the brain involves a high dose to the skin (15.5 mGy for 2 slices) and brain over a narrow slice for each 'cut', and a gonad dose of 0.015 mGy for each two slices (Robinson & Dellagrammaticas, 1983) Two babies had CT of the brain and each had 8 slices on an EMI CT1010 machine, giving skin doses of 62 mGy and gonad doses of 0.06 mGy.

ESTIMATION OF CARCINOGENIC AND GENETIC RISKS

Using Table III and the dose estimates for radiation exposures during cardiac catheterisation and CT given above, together with estimates of the risks attributable to each gray of radiation, it is possible to make estimates of the carcinogenic and genetic risks associated with neonatal radiation. Assuming that the proportions of babies undergoing these procedures are roughly the same throughout the UK, we can estimate the total numbers of cases of cancer and genetic disease which might be caused by these procedures.

Cancer and leukaemia

Data from various sources are available for the estimation of the risks of cancer as a result of exposure to ionising radiation. Much of this has been summarised by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (1972, 1977, 1982). The most relevant results for the present purpose are those reported by Stewart and Kneale (1970) and by Bithell and Stewart (1975) relating to obstetric radiography. These authors present results for what is, in effect, whole-body irradiation of the fetus Bithell and Stewart showed that it was reasonable to assume that the risk of inducing childhood cancer as a result of ante-natal radiography to the fetus is linearly related to the dose, over a range of small doses.

Stewart and Kneale estimated that the risk of childhood cancer (actually death from malignant disease by age 10 years) was 57 cases per thousand gray, this estimate has a standard error of 13.

However, the dose estimates for in-utero exposures used by Stewart and Kneale were not accepted by the authors of the UNSCEAR reports (1972, 1977). They suggest that the dose per radiograph was, on average, more than twice as great as that used by Stewart and Kneale and hence that the risk was less than half their figure, *i.e.*, about 23 cases per 1000 gray with, presumably, a standard error of between five and six.

All of these estimates are based on numbers of deaths occurring before age 10 years included in a case-control study of childhood cancers. When that study was carried out such deaths accounted for about half of all cases of childhood cancer, usually defined as cases diagnosed before age 15 years. If the risk from antenatal radiography extended throughout this age range the above estimates would have to be doubled, Monson and MacMahon (1984) suggest that the association between obstetric radiography and childhood cancer may not extend beyond age nine. (They also suggest that the association may not in any case be a causal one, but for the present purpose we are only concerned with the problem of determining an upper limit for the risk, assuming that it is in fact real).

In estimating the possible numbers of cases of malignant disease attributable to neonatal radiation we have used what we consider to be a reasonable upper limit for the risk, calculated by taking the upper 95% confidence limit of the risk given by UNSCEAR (1972), *i.e.* the estimate plus twice its standard error, 34 cases per 1000 Gy, and then multiplying this by a further factor of 1.5 to allow for cases not dying before age ten, to give an estimate of 51 cases per 1000 Gy. We then calculate the expected numbers of cases of malignant disease among neonates exposed to radiation, using the estimate of total radiation exposure given in Table III, this also involves an overestimation of the risk since the data on obstetric radiography are in effect based on whole-body exposure of the fetus, whereas the neonatal radiography involved only partial-body exposure; it also assumes that the newborn and the fetus are equally susceptible to the carcinogenic effects of radiation. It is not known whether babies in a higher oxygen tension than fetuses run a greater risk of carcinogenesis from radiation.

Radiography excluding cardiac catheterisation and CT. If the above assumptions are accepted the risk attributable to just one chest or abdomen radiograph is $0.07 \times 10^{-3} \times 51 \times 10^{-3}$, *i.e.* 3.6×10^{-6}, or a chance of 1 in 280 000, that malignant disease will be caused The average number of radiographs taken at the John Radcliffe Hospital for babies who had radiography was about 6.5, the average risk associated with radiography is therefore about 1 in 40 000. For 25–30 radiographs, or for fluoroscopy lasting for 1.5 min, the risk becomes about 1 in 10 000. (The dose per radiograph is somewhat higher for the relatively small numbers of babies having skull radiographs) For reasons given above it is unlikely that the risks are as high as those calculated here; we have probably overestimated the risks, first in the allowance made for statistical estimation errors and, secondly, in assuming that the risks arising from the limited X-ray exposures considered here are equivalent to those for whole-body exposures. Higher estimates of the risk would be obtained if we used the original Stewart and Kneale estimates of dose (as did the BERI report, 1980) and if we also assumed that the risk from perinatal radiation exposure extended to age 15 rather than age 10.

Another way of looking at the risks is to estimate the total number of cases of malignant disease that would be caused, making the same assumptions as above, if the experience of the John Radcliffe Hospital as regards exposure of newborn babies to radiation is typical of that for the rest of the UK.

The average radiation dose for the 5488 live-born babies whose mothers lived in the Oxford District and were born at the John Radcliffe Hospital, excluding exposures from cardiac catheterisation and CT, was 0.04 mGy. The current annual total of births in the UK is about 720 000. Thus we estimate that the annual total dose of radiation received by the newborn is about 29 Gy.

On the basis of the estimates of risk already given we might expect between one and two cases of malignant disease per year in the UK to be caused by these exposures. If the percentage of neonates radiographed is 10%, rather than 6.4% as found in the present study, the expected numbers of cases of malignant disease corresponding to the estimated risks given above would be between two and three per year.

The risks from neonatal radiation, excluding cardiac catheterisation and computed tomography may be summarised by saying that:

(i) The average risk, *i.e.* that for an exposure involving six or seven radiographs, from ordinary radiography is unlikely to be greater than 1 in 40 000 and may well be much less.
(ii) The average risk from fluoroscopy (lasting about 6 min) is unlikely to be greater than 1 in 2500, and may well be much less.
(iii) For the whole of the UK we estimate that, at worst, only about two cases of childhood cancer would be caused by neonatal radiation at the levels observed in 1982.

Radiography during cardiac catheterisation. The average skin dose for babies having cardiac catheterisation was 131 mGy. Using the risks given above and assuming that this procedure involves whole-body exposure, the estimated risk of malignant disease is about 1 in 150; if we assume that there is only partial-body exposure the risk is correspondingly less.

We do not know the total number of cardiac catheterisations in the newborn in the UK or the proportion of these babies who survive. Three out of the six babies having cardiac catheterisation at the John Radcliffe Hospital died. If, for instance, we assume that there are 500 cardiac catheterisations each year in the whole of the UK and that 50% of these survive, and using our prediction that at most one in every 150 of these survivors would develop malignant disease, we might expect about two cases to be caused each year among these children. For the same number of catheterisations, and a 90% survival rate we would expect at most about three cases per year.

Radiation from computed tomography. In the current study only two babies had CT of the brain and each received an estimated skin dose of 62 mGy A whole body dose of this magnitude would, on the basis of the risk estimates derived above, have a 1 in 300 chance of causing malignant disease. However, it seems probable that the true risk is considerably lower than this, not only because our risk estimates are probably too high, but also because the doses to other parts of the body resulting from CT scans of the brain are likely to be considerably less than the dose to the skull.

Genetic risks

The radiographic examinations described in this paper usually involved only very small gonadal exposures to radiation and the genetic risks to any subsequent offspring of these babies appear to be very small indeed.

There are no human data available on which to base estimates of the genetic risk resulting from irradiation of germ cells. Indirect methods of estimating the risks, and values for the estimates so obtained, are presented in the UNSCEAR reports and also in the report prepared by the (US) Committee on the Biological Effects of Ionizing Radiations (the BEIR report, 1980). These reports give estimates of the incidence of various types of genetic damage from specified population exposures to radiation, both for the first generation after exposure, and the 'equilibrium' rate assuming that successive generations are exposed at the same level.

The BEIR report, which gives slightly higher estimates than the UNSCEAR report for the increase in genetic risk for the first generation, and considerably higher estimates for the equilibrium increase in risk, suggests that an average population exposure of 10 mGy (one rad) could result in an increased incidence of serious genetic disorders of between 5 and 75 per million births in the first generation and about 60 to 1100 per million when the rate is in equilibrium, *i.e.*, assuming that this level of exposure continues through successive generations. (The wide range in values reflects the lack of information available in making these estimates).

We can make a rough, but, for the present purpose, adequate, estimate of the average gonadal dose for the 5488 babies included in this study as follows:

TABLE IV

ESTIMATION OF TOTAL GONAD DOSES FROM RADIOGRAPHY AND SCREENING

Examination	Gonad dose per radiograph* (mGy)	Number of radiographs	Total gonad dose (mGy)
Chest AP	0.00114	1547	1.94
Chest lateral		159	
Chest and abdomen		363	
Abdomen	0.041	105	23.82
Skull and other		113	
5% addition for spoilt films			1.29
Skin dose from fluoroscopy (45.5 mGy) of which the gonad dose is approximately 45%			20.48
		Total gonad dose	47.53

*Using estimates given by Robinson and Dellagrammaticas (1983), Table I, and assuming that 'Skull and other' radiographs give on average the same gonadal exposure as abdominal radiographs.

Table IV shows the gonad doses for various types of radiograph and for screening, together with the total numbers/time of exposures for each type. The final column of this table gives the total gonad doses for each type and the grand total for all 5488 babies, *i.e.*, 47.53 mGy. To this must be added the exposures for the two patients having CT, 0.12 mGy (Robinson & Dellagramaticas, 1983) giving a total of 47.65 mGy. Thus excluding the patients who had cardiac catheterisation, the average gonadal dose was 0.009 mGy, or approximately one-thousandth of a rad, less than 1% of the annual dose from background radiation. Even on the most pessimistic of the estimates given in the BEIR and UNSCEAR reports, and assuming that the genetic effects on the newborn are similar to those for adults, this would lead to an increased incidence of serious genetic disorders amounting to less than one in ten million in the first generation and, if similar procedures continued indefinitely, to one in one million in subsequent generations.

We have no information on the gonadal dose received during cardiac catheterisation, but if we assume that it is the same same as the skin dose, and assuming that half of these babies survive, the figure of 47.65 mGy becomes 441 mGy, an approximate ten-fold increase, with corresponding increases in the risk of genetic disorders estimated above.

DISCUSSION

Radiographs are most commonly taken in the neonatal period to assist in the diagnosis and management of respiratory difficulties; to see, for example; if there is a pneumothorax or a collapsed segment of lung, to note the position of the umbilical arterial catheter or to note the position of an endotracheal tube. Frequent accurate radiographic assessment is required and the risks of not radiographing such patients must be balanced against the risks of inducing childhood cancer or genetic defects. Sixteen of the 18 babies who had 25 or more radiographs (average 59) were premature and suffered from respiratory distress syndrome sufficiently severe to require ventilation. The average risk of developing neoplasia from such radiation is unlikely to be greater than one in 4700. This is a very low risk when compared to the 19% mortality reported by Greenough and Roberton (1985) in such babies.

For example, in 1982 in the SCBU at the John Radcliffe Hospital 21 babies had pneumothoraces and three babies had pneumomediastinums diagnosed by radiography. Sixteen of these babies survived and it is likely that there would have been fewer survivors without the aid of radiography. While coldlight transillumination may be used in an emergency to confirm the presence of a pneumothorax, it is unlikely that the technique will become sufficiently refined to replace radiography.

The risk of radiation to the newborn is minimised by making sure that only essential radiographs are taken, that accurate coning confines radiation to the relevant part of the infant, that radiation shields over the lower abdomen are used unless this area is to be included on the radiograph, and that adequately trained staff perform the radiographs so that the number of repeat radiographs is reduced to the absolute minimum. The risk could be further reduced by using rare-earth screens (Wesenberg et al, 1977) provided that a portable X-ray machine was available which was capable of making the short exposures required.

Needless to say, the arguments presented here give no grounds for unnecessary radiography of the newborn but they do suggest that if such radiography is regarded as clinically necessary the cancer hazard should not be used as a strong argument for avoiding such radiographs If the radiography used at the John Radcliffe Hospital is a reflection of the country as a whole then, excluding radiation from cardiac catheterisation and CT, it is unlikely that irradiation of the newborn will cause more than one case of childhood cancer per year among babies born in the UK, and the risk may well be less than this. The risk of developing malignancy from a single radiograph is unlikely to be more than one in 280 000.

For cardiac catheterisations and CT the doses and the corresponding risks may well be considerably higher than for other forms of radiography but are probably much lower than we have suggested above, since we have assumed that the doses are whole-body doses whereas this is obviously not the case. We would also emphasise that the numbers of cases are small, and that, at least for cardiac catheterisation, the risk is probably small in comparison with the other risks inherent in the procedure or with those involved in not carrying it out. Spengler et al (1983) found no excess of cancer deaths among a group of 4891 patients irradiated during cardiac catheterisation (80% of these were below age 10 and nearly all were below age 20). Follow-up was an average of 13 years after the time of catheterisation but the authors did not know how many of these patients died from other causes during the period—if this number were large it would cast some doubt on their findings.

Ultrasonography is replacing much cardiac catheterisation, but when catheterisation is required the risks, albeit small, of diagnostic radiation should be taken into account Similarly, ultrasonic sector scanners have replaced CT in most examinations of newborn brain; the skin dose from CT is high enough to make strict selection of patients necessary, especially as the brain is still developing in the newborn (Mole, 1979; Otake & Schull, 1984). Very few cases of mental retardation have been shown in fetuses of more than 26 weeks gestation exposed to less than 500 mGy of absorbed radiation (Otake & Schull, 1984).

For any of the investigations considered here the risks of serious genetic disorder in subsequent generations appear on the best available estimates, to be negligible.

Thus, while radiography for newborn infants should be performed with full knowledge of the possible harmful effects, the risks of not using it in intensive care of the newborn outweigh the risks of either cancer or genetic disease

ACKNOWLEDGMENTS

We thank Mrs Ann Dixon-Brown for performing the radiation measurements, and Mrs Eileen Hickling for preparing the manuscript The Childhood Cancer Research Group is supported by the D H.S S. and the Scottish Home and Health Department.

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Book reviews

Imaging in Pediatric Oncology. Ed. by J. H. Miller, pp. xvi+521, 1985 (Williams & Wilkins, Baltimore, Maryland), £70.00.
ISBN 0–683–05978–5

This is a very comprehensive review of the various methods available to delineate childhood neoplasms In particular, the place of the more sophisticated techniques available is reviewed with an attempt to define their advantages and limitations. Much of the text is, therefore, taken up with nuclear medicine, ultrasonography and computed tomography, while conventional, simpler forms of radiography and angiography are considered only in relation to specifically relevant situations.

The chief editor has been joined by numerous clinical colleagues for detailed discussions and evaluation of tumours occurring in the various anatomical systems. Two introductory chapters discuss clinical relevance of imaging and introduce the various techniques available with particular reference to practical considerations and patient preparation. The final section is a compilation of complications of cancer therapy and also of those due to associated infection

The text is very comprehensive and the illustrations many and, generally, of excellent clarity In addition to detailed descriptions of findings and techniques, an attempt is made to provide a logical sequence of investigation for each particular tumour so that the most effective use of the various methods is ensured and as little distress as possible is experienced by the unfortunate patient.

References are profuse and augment the usefulness of this excellent reference text.

D. G. Shaw

Ultrasound of the Infant Brain. By Malcolm I. Levene, Jonathan L Williams and Claire-Lise Fawer, pp. x+148, 1985 (Blackwell Scientific, Oxford), £12 50
ISBN 0–632–01327–3

This is a worthwhile addition to English textbooks on echoencephalography It is Volume 92 in the series "Clinics in Developmental Medicine" The three authors are English and Swiss neonatologists and an American paediatric radiologist who have all produced notable papers on echoencephalography in recent years. Their aim was to provide an introduction to a fascinating and valuable technique to novice ultrasonographers and to share their own considerable experience with those already practising the art This admirable, easily read book accomplishes their aims, although some of the 200 illustrations require imagination to appreciate the legends The clinico-pathological correlation is excellent and the place of echoencephalography in neonatal practice established with claims for its present position being modestly understated in relation to the other new imaging techniques. An adequate, simple introduction to ultrasound is followed by an excellent chapter on technique and normal anatomy There is then a series of short chapters dealing with pathology likely to be encountered in the infant brain and spinal cord which can be imaged by ultrasound, showing how demonstration of haemorrhage and ischaemic lesions has helped in understanding the sequence of pathological processes whose results had been demonstrated by morbid anatomists. This book can be recommended to all concerned with the practice and interpretation of encephalography in maternity hospitals and paediatric units. Its modest size makes it an ideal "bench-book" to be kept beside the real-time machine in the special-care nursery The index is good and each chapter has a well chosen list of references to recent literature It is a measure of the speed of development in new imaging techniques that we now look forward to volumes on Doppler ultrasound and magnetic resonance imaging to follow this one to further our understanding of the infant brain

Elizabeth M Sweet

Pediatric Nuclear Medicine By S T. Treves, pp. xxiv+338, 1985 (Springer-Verlag, Berlin), DM 240.00.
ISBN 3–540–96001–5

Paediatric nuclear medicine has differentiated from the general practice of adult nuclear medicine, so this very comprehensive text from the Children's Hospital and Harvard Medical School in Boston is particularly welcome The author has been joined by numerous colleagues, whose special interests cover the wide variety of organs and techniques discussed

Each chapter considers the radiopharmaceuticals and examination technique in detail and then proceeds with the clinical applications. In addition to broad subjects, such as the examination of bone, kidneys, liver and spleen, thyroid, brain, heart and lung, less widely known applications of nuclear medicine, such as the assessment of mandibular growth and asymmetry and of vesico-ureteric reflux Scrotal disease and dacryoscintigraphy are also considered The text is clear, the illustrations profuse and each chapter has an extensive bibliography This book will be of considerable interest to those departments which carry out relatively few paediatric investigations or where the institution of a particular technique for children is contemplated

D G. Shaw

Case reports

Complete regression of pulmonary metastases from malignant melanoma of the vulva following therapy with tamoxifen

By Rajni Amin, M.B.B.S., M.R.C.P., F.R.C.R., D.M.R.T.

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(*Received June 1985*)

A case is reported with pulmonary metastases from malignant melanoma of the vulva, in which response to tamoxifen was observed after 6 months of continuous therapy, and complete response was still maintained after 29 months of therapy.

CASE REPORT

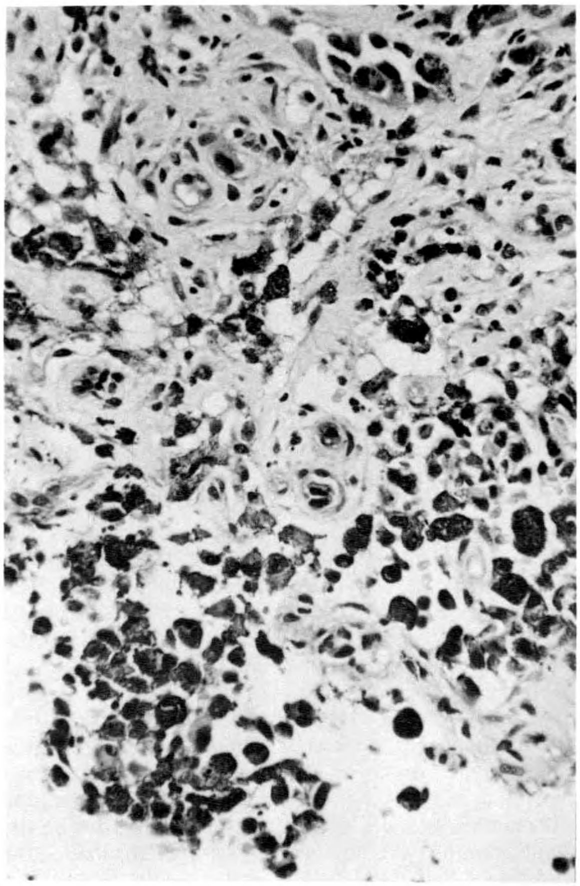
An 81-year-old woman presented in June 1982 with a few weeks' history of pigmented lumps on her vulva. She had no other symptoms. On examination, extensive pigmentation of the vulva, with several deeply pigmented dark nodules, was found. Biopsy of one of the nodules showed ulcerated malignant melanoma with many heavily pigmented tumour cells (Fig. 1). A full blood count, biochemical profile and a chest radiograph were normal. She underwent radical vulvectomy in July 1982. Thereafter, she remained well until October 1982, when a 1.0 cm recurrence was noted at the introitus. At this stage she was referred to the Radiation Oncology Clinic. Investigations now showed a normal full blood count. Biochemical profile showed deranged liver function tests. Chest radiography revealed several small metastases in both lung fields and a larger deposit in the left lower zone (Fig. 2). Computed tomography of the abdomen and pelvis showed no abnormality in the abdomen, but in the pelvis there was a soft-tissue mass just anterior to the rectum. It was decided to treat this woman with cytotoxic therapy, but she declined to undergo chemotherapy. A month later she developed urinary incontinence, with pain and bleeding from the recurrence at the introitus. She was now considered for local radiation therapy. An incident dose of 6000 cGy was prescribed on a telecobalt unit, using a port size of 8 cm × 8 cm. In all, she received 26 fractions over 46 days.

In February 1983 her symptoms were relieved, but there was no apparent regression in the size of recurrence at the introitus. A month later the recurrence at the introitus had grown to 2.0 cm and there was further increase in the size and number of metastases in the lungs. She still did not wish to undergo cytotoxic chemotherapy, so she started treatment with tamoxifen (an anti-oestrogen agent), 20 mg twice daily.

In May 1983 the lesion at the introitus was stable, but there appeared another pigmented lesion, about 1.0 cm in size, just to the right of the introitus. Chest radiography showed further increase in the size of the smaller metastases, but the larger deposit in the left lower zone was marginally smaller. Liver function tests were normal now. Treatment with tamoxifen was continued and it was not until September 1983 that the pigmented lesion to the right of the introitus started to regress. Chest radiography showed regression of the smaller metastases.

In December 1983, all of the smaller metastases in both lung fields had practically regressed and there was further diminution in the size of the left lower-zone metastasis. Thereafter, all of the recurrences started to regress slowly and, by December 1984, a chest radiograph was normal (Fig. 3). The recurrence at the introitus had regressed in size to 1.0 cm and the one to the right of the introitus had shrunk to a size of 3 mm.

At her last review, in August 1985, she was completely asymptomatic, with no further evidence of recurrence and a normal chest radiograph. She continues on tamoxifen.



Section showing ulcerated malignant melanoma with many heavily pigmented tumour cells (HE × 125).

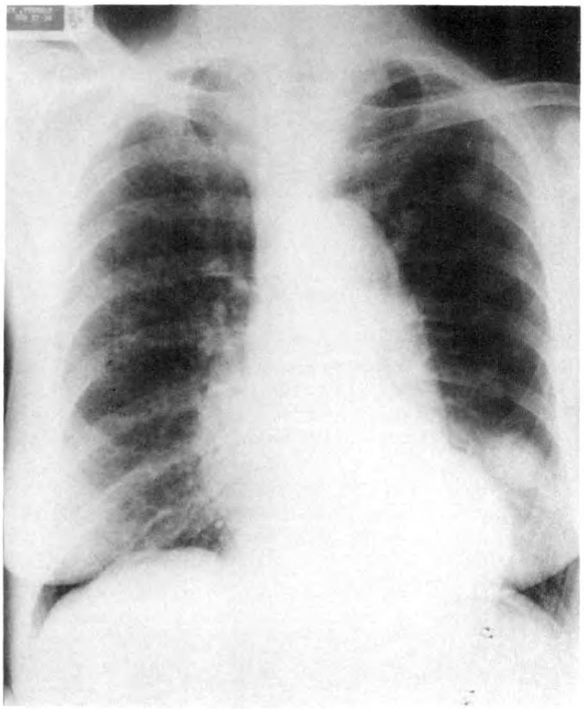


FIG. 2.
Chest radiograph showing several small metastases in both the lung fields, with a larger deposit in the left lower zone.

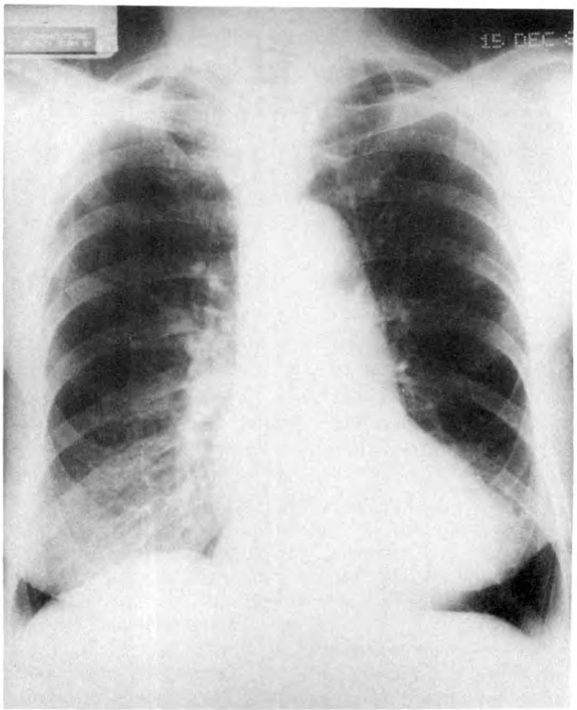


FIG. 3.
Chest radiograph showing normal appearance.

DISCUSSION

The role of steroid hormones in the growth and spread of human malignant melanoma has long been the subject of considerable interest. The identification of oestrogen receptors in malignant melanoma by Fisher et al (1976) raised the possibility of hormonal manipulation in an identifiable subset of patients with disseminated melanoma.

Several clinical trials have shown that various endocrine manipulations can benefit some patients with advanced disease (Didolkar et al, 1978; Nesbit et al, 1979; Meyskens & Voakes, 1980; Papac et al, 1980; Karakousis et al, 1980; Masiel et al, 1981; Mirimanoff et al, 1981; Reimer et al, 1982; Papac and Kirkwood, 1983). However, remissions have been short-lived and have usually been partial.

Mirimanoff et al (1981) reported a patient who was free of disease for more than 28 months after tamoxifen was started for local recurrence. This case report records a second long-term survivor following therapy with tamoxifen. It is interesting to note that during the first 9 months of treatment with tamoxifen some of the metastases had continued to grow, whilst others had started to regress. It was only after continued therapy of longer than 9 months that all the metastases started to regress. Prolonged administration of tamoxifen is well tolerated and does not appear to be associated with serious side-effects.

Malignant melanoma has a variable biological behaviour pattern and metastases do not grow at a fixed rate. Treatment should, therefore, be continued for longer periods, provided the condition of the patient is stable.

ACKNOWLEDGMENT

I wish to thank Dr P. P. Anthony for his help with the photomicrograph and interpretation of the histology.

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Erdheim–Chester disease presenting as malignant exophthalmos

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In 1930, Chester working with Erdheim described a lipidosis which he distinguished from other lipogranulomatoses (Chester, 1931). Jaffe (1972) reported a similar case which he called "Erdheim–Chester disease". Since then, few observations have been published.

We report a further case of Erdheim–Chester disease presenting with bilateral proptosis. Clinical examination was completed by immunological tests, orbital and body CT, bone scan, and histopathology with electron microscopy.

The course of the disease was slowed by treatment during a two-year period.

CASE REPORT

A 57-year-old caucasian man was admitted because of bilateral proptosis with recent and sudden diminution of visual acuity in the right eye. Exophthalmos had been noted three years earlier and the patient had been treated with prednisone The proptosis was fluctuating. There was no previous medical history, except for mild untreated hypertension. He had gained 4 kg in weight over the previous three years There were no skeletal symptoms.

On admission, bilateral proptosis was spectacular and associated with chemosis. There was neither upperlid retraction nor ocular eyelid asynergy. Exophthalmos measured with Hertel's exophthalmometer was above 40 mm in both eyes

Other physical findings included: height 1.72 m; weight 76 kg; temperature = 38°C, blood pressure 170/90 mm; heart rate 84/min; hepatomegaly, splenomegaly, bilateral kidney enlargement, and oedema of the lower extremities. Pertinent negative findings included a normal thyroid gland, no palpable adenopathy, and no skeletal abnormalities Laboratory tests are recorded in Tables I and II. ECG, echocardiography, and chest radiographs were normal.

Orbital computed tomography revealed bilateral intraorbital densities sheathing both optic nerves and deforming the inner orbital walls (Fig. 1). Radiography of the skull was normal. A right orbital biopsy was done.

TABLE I

HAEMATOLOGY AND BIOCHEMISTRY

Blood	
White blood cell count 14 3 10.9/1	
Differential count. neutrophil polynuclear 80%, lymphocytes 16%, monocytes 4%	
Red cell count 4 98 10.12/1	
Haematocrit 42%	
Haemoglobin 13 7 g/100 ml	
Erythrocyte sedimentation rate 19 mm	
Platelets 623 10.9/1	
Bone marrow biospy normal	
Plasma	
Creatinine	83 μmol/1
Calcium	2.27 mmol/l
Phosphate	1.3 mmol/l
Alkaline phosphatase	77 IU/l
Glucose	9.1 mmol/l
Cholesterol	3.5 mmol/l
Triglycerides	1.45 mmol/l
Proteinuria	absent
C.S.F.	normal

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TABLE II

THYROID FUNCTION TESTS, INFLAMMATION TESTS, IMMUNOLOGICAL TESTS

Thyroid function tests		
T4	6.7 μg/100 ml	(*N* = 4–12)
ITL4	2.5%	(*N* = 1.2–4.8)
T3	78 ng/100 ml	(*N* = 80–200)
TSH response during a TRH test was normal		
Antithyroglobulin, antimicrosomial antibodies research was negative		
TSI normal		
Serum		
Total protein	43 g/l	(*N*: 61–75)
Albumin	23.9 g/l	(*N*: 35–45)
Ferritin	347 μg/l	(*N* = 50–180 μg/l)
Immunological test		
IgG	640 mg/100 ml	(*N* = 610–1420)
IgA	194 mg/100 ml	(*N* = 130–400)
IgM	41 mg/100 ml	(*N* = 60–220)
Complement C3–C4 levels were normal.		
Immune circulating complexes present.		

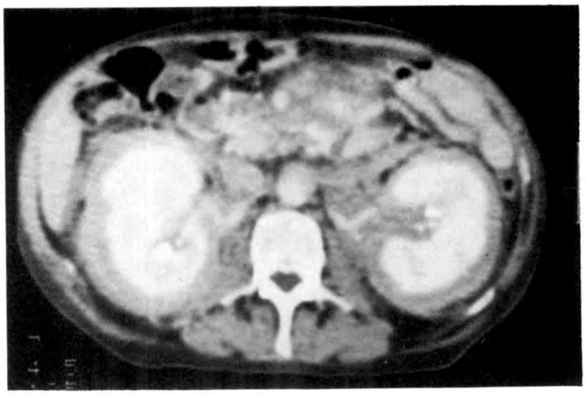

FIG. 2.

Body CT. Retroperitoneal and viscera diffuse infiltration.

Computed tomography (CT) showed diffuse infiltration involving the mediastinum, retroperitoneal space, kidneys, adrenals and pelvis (Fig. 2). An intravenous pyelogram revealed strangulation of calyces and proximal ureters with proximal dilatation, findings usually described in sinus lipomatosis (Fig. 3). Biopsy of the perirenal infiltration was performed under CT control. Skeletal radiography showed widespread symmetrical areas of sclerosis in the long tubular bones and increased bone density with thickening of trabeculae. Periostal new bone formation was found adjacent to the areas of sclerosis in the humeri, femora, and fibulae, resulting in cortical thickening (Fig. 4A, B).

A radionuclide bone scan with $^{99}Tc^{m}$ pyrophosphate showed an increased deposition of radioactivity in sites corresponding to areas of increased radiographic density. A strong orbital uptake was also seen (Fig. 5).

Pathological findings were as follows. Specimens obtained from the orbital retro-ocular mass were yellow with a homogeneous, fatty, butter-like gross appearance. Microscopic examination showed large areas of foamy histiocytic cells with intracytoplasmic lipoid vacuoles. Histiocytes were mixed with polymorphous inflammatory cells and associated with a variable amount of fibrosis. There were neither mitoses nor atypical cells.

A biopsy obtained from the retroperitoneal mass showed a similar microscopic appearance. Electronic microscopy of the retro-ocular mass demonstrated active phagocytosis in large, clear histiocytes (Fig. 6). X-bodies could not be found on electromicroscope studies.

The patient was treated with vinblastine (0.1 mg/kg body weight weekly) and prednisone (1 mg/kg body weight daily). This treatment resulted immediately in a return to normal

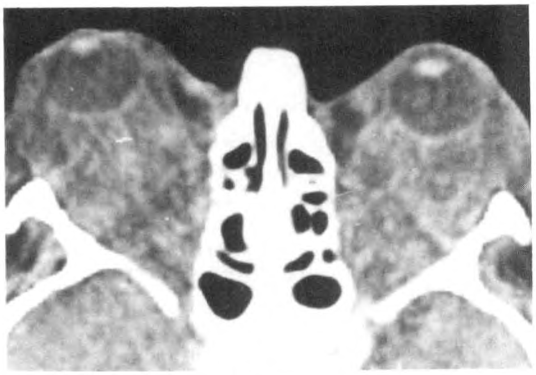

FIG. 1.

Orbital CT. Bilateral proptosis. Dense infiltrative process sheathing both optic nerves and deforming inner orbital walls.

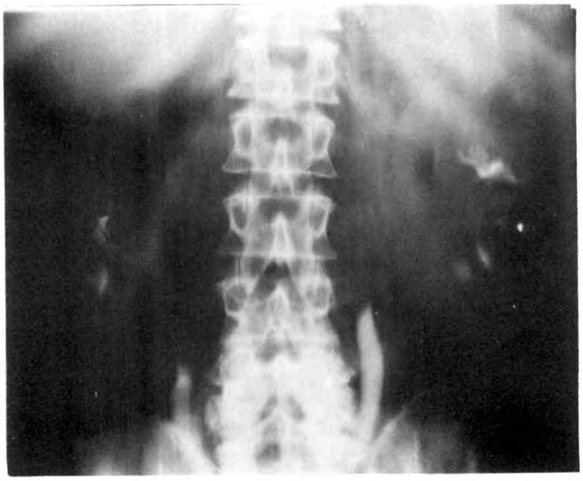

FIG. 3.

Intravenous pyelogram. Strangulation of calyces and proximal ureters but with distal dilatation.

temperature, improvement of the patient's visual acuity, and decrease of the proptosis. After the sixth dose of vinblastine dose, measurement with Hertel's exophthalmometer was 34 mm for the right eye, and 36 mm for the left eye. A CT scan revealed a 50% decrease in the amount of retroperitoneal infiltrate (Fig. 7).

Nevertheless, the patient died two years later, with acute meningoencephalitic signs which were apparently related to an intercurrent infection. An autopsy was not allowed.

DISCUSSION

Erdheim–Chester disease is included in the lipogranulomatoses but distinction from conditions related to histiocytosis X, particularly Hand–Schuller–Christian disease, may be difficult, although there are some helpful distinguishing signs. In the latter condition, the bone lesions are lytic, asymmetrical with frequent location in the skull and spinal column (Moseley, 1962); in addition, X-bodies are demonstrated in histiocytes on electron microscopy. In contradistinction, the bone lesions of Erdheim–Chester disease consist of symmetrical, diffuse osteosclerosis of the long bones and there are no X-bodies in the histiocytes. Other normolipaemic lipidoses include xanthoma disseminatum where iris and visceral deposits are possible, but this condition affects young people, and is always associated with skin lesions (Beurey et al, 1979). In multicentric reticulohistiocytosis, a tumour-like histiocytic infiltration with foamy giant cells is described, sometimes affecting the eye, but the main features are skin and joint involvement (Sachs et al, 1983). Oberling (1935) designated retroperitoneal xanthogranuloma as a pathological entity comprising foamy histiocytic proliferation with polymorphous granulomas and fibrosis. The author regarded this as a benign local inflammatory process but a more recent review of literature (Kahn, 1973) demonstrated that cases reported as retroperitoneal xanthogranuloma included potentially malignant neoplasms.

In seven previously described cases of Erdheim–Chester disease, retroperitoneal lipoxanthogranulomatosis was found (Chester, 1931—2 cases; Dietrich, 1913; Melicow, 1953; Resnick et al, 1982—3 cases). In addition, two cases of retroperitoneal xanthogranuloma associated with lipid granulomatosis and bone lesions have been described (Melicow, 1953; Simpson et al, 1978). This association of such rare conditions suggests a common underlying pathology.

Malignant exophthalmos was the initial symptom in our case. Orbital computed tomographic findings were distinct from those of orbital pseudotumours (Garner, 1975; Enzmann et al, 1976; Chavis et al, 1978; Forbes et al, 1980; Sergott et al, 1981; Nugent et al, 1981).

The diagnosis of Erdheim–Chester disease was based upon the following positive findings: hepatomegaly, splenomegaly, enlarged kidneys, radiological retroperitoneal mass, bilateral osteosclerosis of long tubular bones, and histological xanthogranuloma.

In conclusion, our case report is the thirteenth example of Erdheim–Chester disease (Dietrich, 1913;

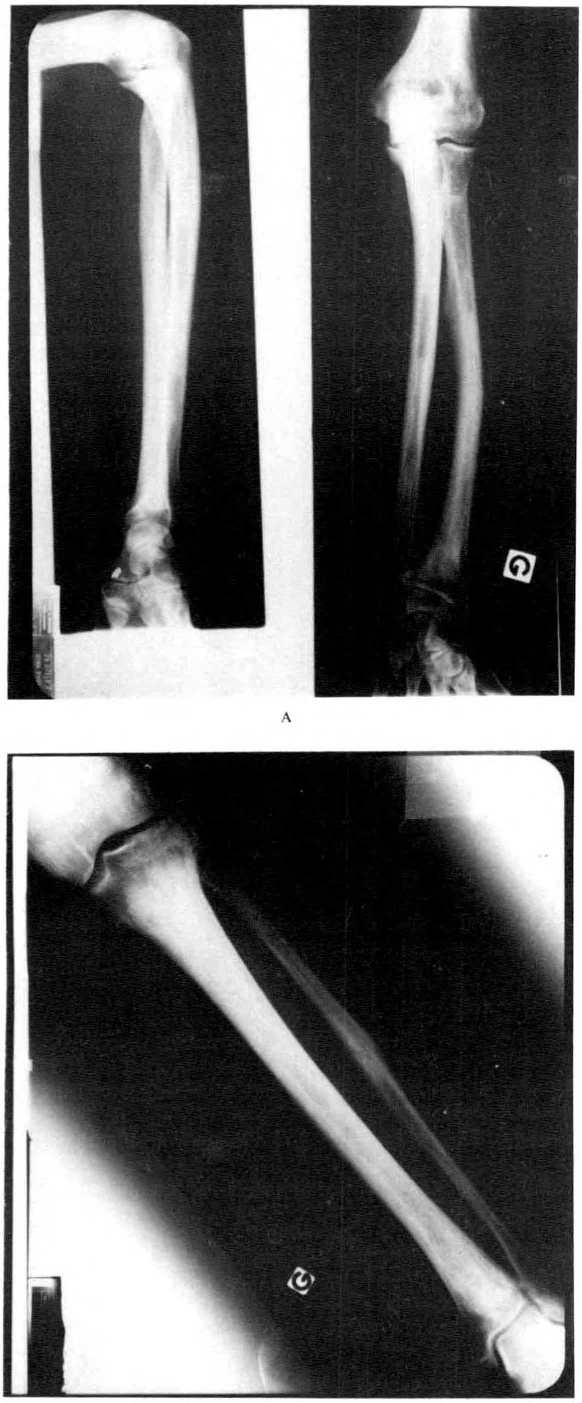

FIG. 4.

(A) Left radius and ulna. Patchy sclerosis involving the metaphysis and diaphysis;

(B) Left tibia and fibula. Patchy sclerosis involving the metaphysis and diaphysis.

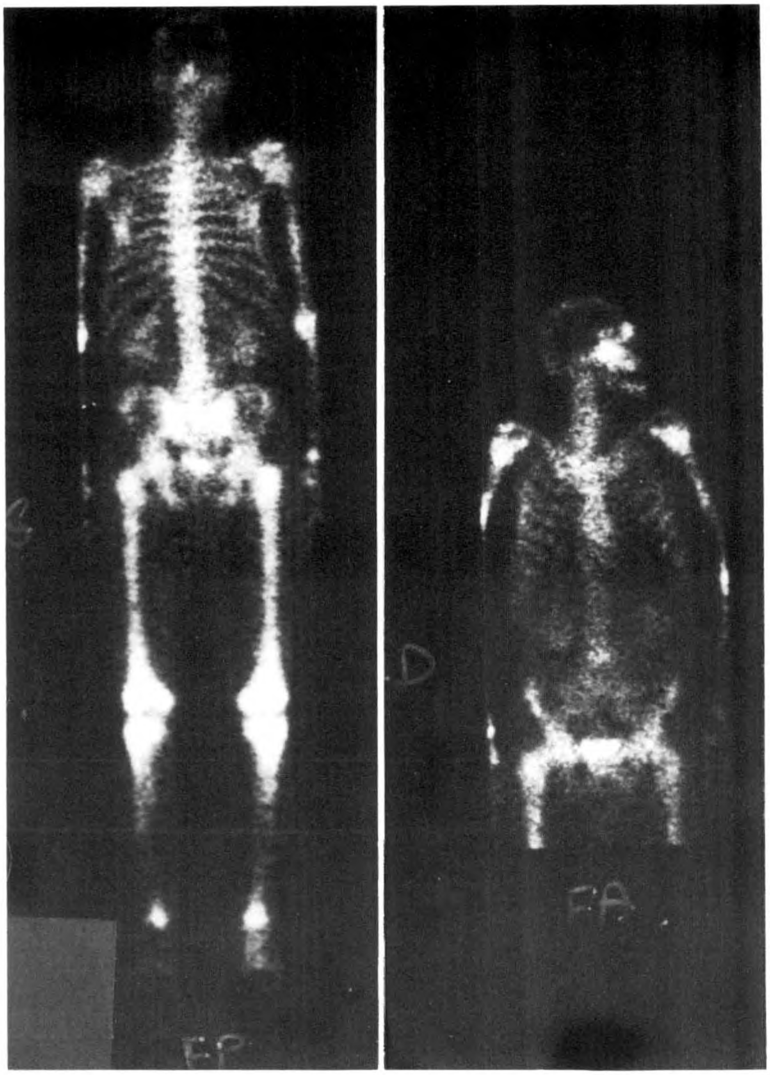

FIG. 5.

Bone scan. Increased deposition in sites corresponding to those of increased radiographic density and strong orbital uptake.

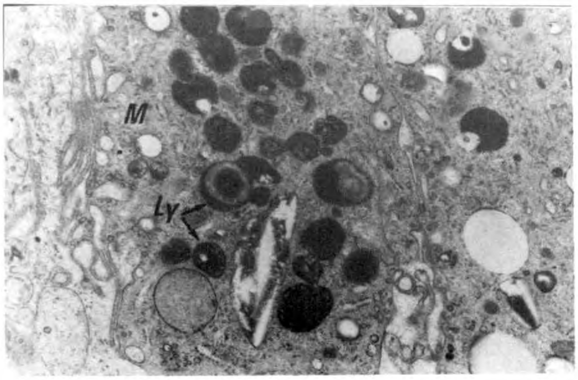

FIG. 6.

Electron microscopy of the retroperitoneal mass. Large, clear histiocytes with evidence of active phagocytosis. Lack of X bodies. M = macrophage. Ly = lysozome.

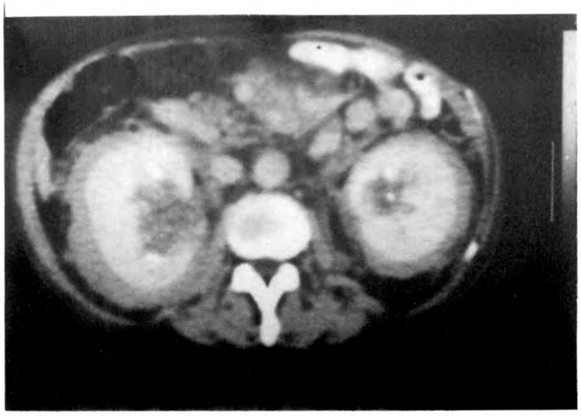

FIG. 7.

CT under treatment. 50% decrease of the abdominal visceral infiltration and the retroperitoneal mass.

Chester, 1931; Melicow, 1953; Sorensen, 1964; Jaffe, 1972; Atkins et al, 1978; Simpson et al, 1979; Dee et al, 1980, Resnick et al, 1982) and the second case in the literature presenting with proptosis (Dietrich, 1913). Immunological tests, isotope bone scan and electron microscopy were performed for the first time in the diagnosis of the condition. As in all cases in the literature, the outcome was fatal, but the diagnosis was made in the living patient, and this is the second example of the evolution of the illness being modified by treatment (Resnick et al, 1982). Regression of visceral infiltration was confirmed by CT scanning.

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Case reports

Altered anterior axillary fold in radical mastectomy still present after breast reconstruction

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The most obvious sign of a mastectomy on a frontal chest radiograph is an absent breast shadow with increased transradiancy of the hemithorax. Another sign seen only in radical mastectomy is a re-fashioned anterior axillary fold, following clearance of the pectoral muscles, which runs upwards and inwards across the chest wall instead of curving downwards on to the breast (Pierce & Grainger, 1980). Breast reconstruction with an implant of soft-tissue transradiancy replaces the absent breast with one which can appear identical on the chest film. However, where it follows radical mastectomy the altered anterior axillary fold remains as the only evidence of breast surgery, and two examples are reported.

CASE REPORTS

Case 1

A 34-year-old woman had a left radical mastectomy in 1979 (Fig. 1). Five years later the breast was reconstructed using a latissimus dorsi flap and a silicone implant; she also had a reduction mammoplasty on her pendulous right breast. The post-operative PA chest radiograph is shown in Fig. 2.

Case 2

A 44-year-old woman had a left radical mastectomy with radiotherapy in 1966. Eighteen years later the breast was reconstructed in the same way as in Case 1. A close-up radiograph of the left anterior axillary fold afterwards is shown in Fig. 3.

DISCUSSION

Patients surviving radical mastectomy, once a standard treatment of breast carcinoma, can now be offered reconstructive surgery. This was previously difficult because of the large skin and soft-tissue defect on the anterior chest wall, sometimes complicated by radiation damage. Reconstruction can be done with a latissimus dorsi myocutaneous flap brought forward on to this area with a silicone prosthesis placed under the flap (Thomas, 1983). The resulting scar can be covered by the back of a brassière, and most patients are satisfied with the new "breast", which gives the radiographic appearances shown here. The reconstruction is often combined with minor cosmetic surgery on the other breast to give a symmetrical appearance. Afterwards, further surgery is possible to give an even more natural appearance, but is not usually considered necessary. Another method of reconstruction relocates on to the chest a portion of the rectus abdominus muscle as a myocutaneous flap with surplus fat and skin from the abdomen. This has the advantage that a silicone prosthesis is not usually necessary (Hartrampf et al, 1982). Reconstruction does not generally involve the axilla, so the altered anterior axillary fold can be expected to remain as a sign of radical mastectomy after this technique also.

These cases highlight the importance of the altered anterior axillary fold on the frontal chest radiograph, as in the absence of adequate history it may be the only evidence of past breast cancer and radical mastectomy. Even without breast reconstruction, it is a useful sign as an absent breast may not be noticed if the contralateral breast shadow is small. However, as there is no reconstructed breast to compensate for the absent soft tissue, the ipsilateral hemithorax remains

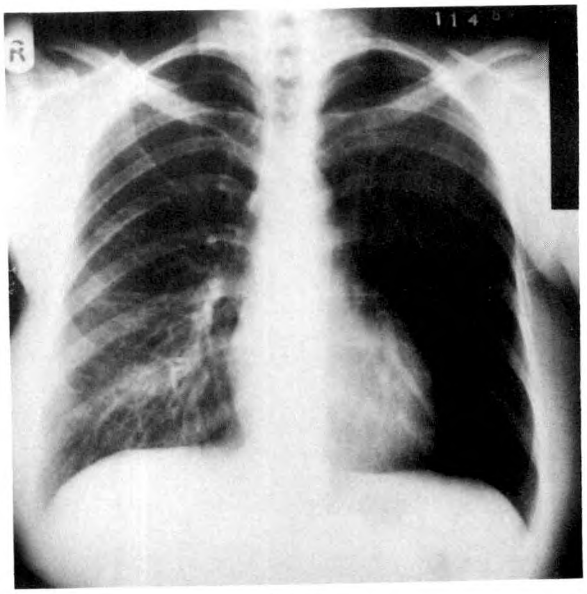

FIG. 1

Case 1: PA chest radiograph showing features of radical mastectomy; absent breast shadow and altered anterior axillary fold. Otherwise the radiograph is normal.

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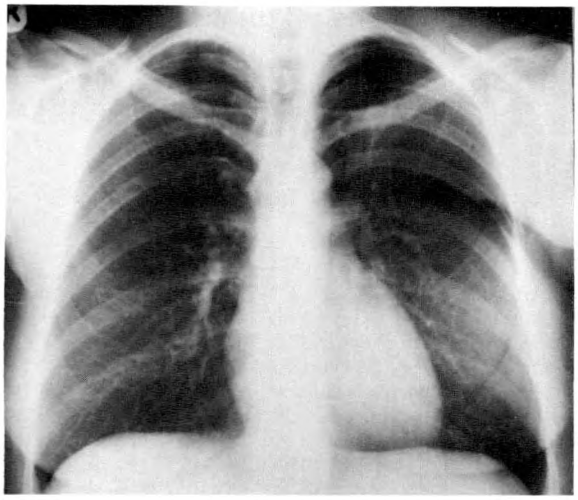

FIG. 2.

Case 1: PA chest radiograph after reconstruction. Only the altered anterior axillary fold remains.

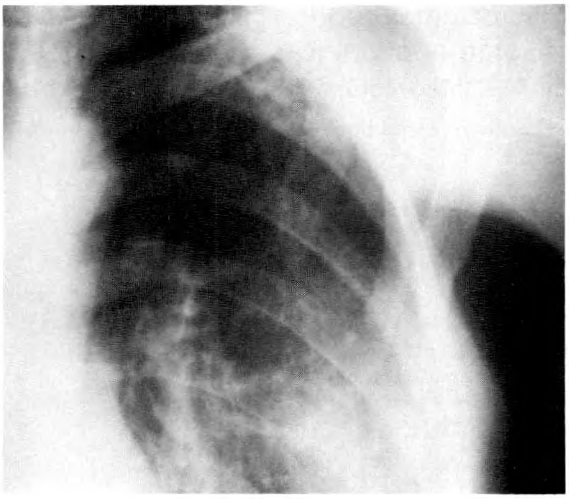

FIG. 3.

Case 2: close-up radiograph showing left anterior axillary fold after breast reconstruction. There are also radiation changes in the left apex. Otherwise the chest radiograph appeared normal.

more transradiant. An "altered" anterior axillary fold with a more transradiant hemithorax is also seen in congenital absence of the pectoralis major (Keats, 1984), which is itself of note as it is occasionally associated with ipsilateral upper limb anomalies (Poland syndrome) sometimes combined with congenital heart defects (Holt-Oram syndrome) or neurofacial anomalies (Möbius syndrome) (Taybi, 1983). In bilateral mastectomies, both sides of the chest appear equally transradiant and the bilateral, altered anterior axillary folds may be diagnostic. Bilateral simple mastectomies, like breast reconstruction after simple mastectomy, are not easily detected on frontal chest radiographs.

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Case reports

Disc calcification in childhood: computed tomographic and magnetic resonance imaging appearances

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Calcification of the intervertebral discs in childhood is an unusual but well described condition (Newton, 1958; Melnick & Silverman, 1963). We report such a case with herniation of one of the two adjacent calcified cervical discs examined by CT and magnetic resonance imaging (MRI).

CASE REPORT

A previously well 9-year-old girl presented with a 6-months history of intermittent neck and left arm pain following a gymnastic injury. There had been no limb weakness, other sensory disturbance or constitutional upset. Physical examination revealed pain-limited restriction of all neck movements but no other abnormality. In particular, there were no abnormal neurological signs.

Initial radiological investigation included plain radiographs of the cervical spine which showed calcification of the C6–7 and C7–T1 intervertebral discs (Fig. 1). In addition, on the oblique projection, calcific material occupying the left neural foramen at the higher level was noted. Computed tomography (IGE CT/T 8800) confirmed dense calcification of the nucleus pulposus of both C6–C7 and C7–T1 discs (Fig. 2) and at the C6–C7 level demonstrated herniation of the nucleus pulposus through a ruptured annulus and into the left C6 neural foramen, displacing the spinal cord (Fig. 3).

Magnetic resonance imaging was performed on a superconducting magnet operating at 0.26 T. The head coil was utilised and images of the cervical spine were obtained in the orthogonal planes which included two eight-image multisection sequences of T_1 and T_2 weightings. There was a diminished signal intensity on both the T_1 and T_2 weighted images from the nucleus pulposus of the C7–T1 disc and, to a lesser extent, the C6–C7 disc (Fig. 4A).

In the position of the left C6 neural foramen there was, again, a region of reduced signal intensity, reflecting the low proton density of the herniated calcific nucleus pulposes (Fig. 4B).

DISCUSSION

Disc calcification in childhood usually involves the lower cervical spine, and the average age of those affected is 8 years (Young, 1980). The exact cause of the

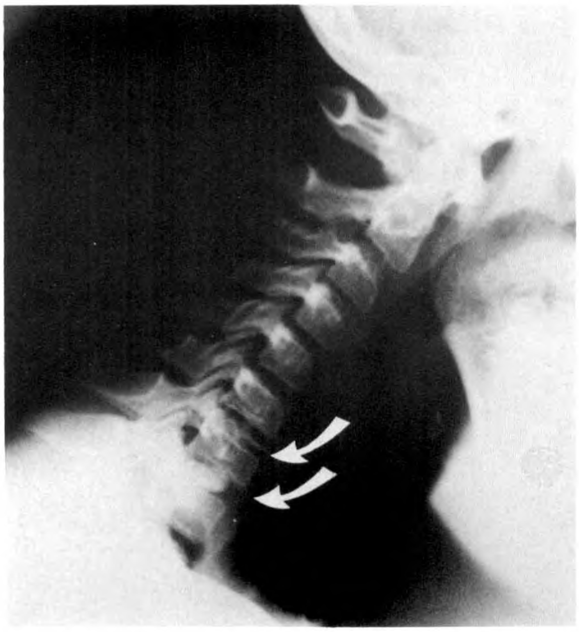

FIG. 1.

Cervical spine (lateral projection) showing disc calcification at C6–C7 and C7–T1 levels (arrows).

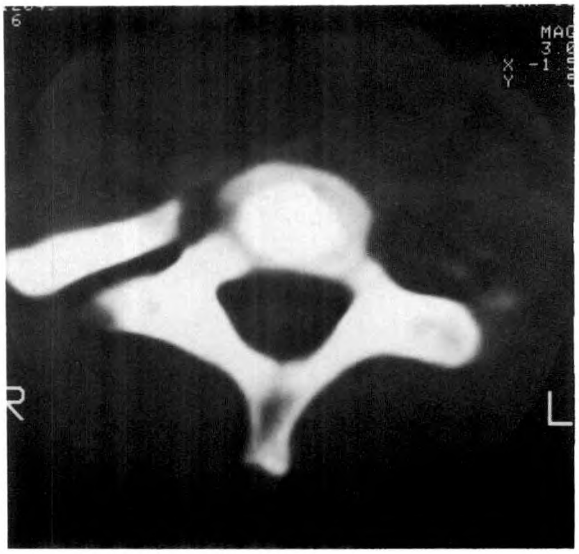

FIG. 2.

A CT scan (C7–T1 level) shows calcification in the nucleus pulposus without evidence of herniation.

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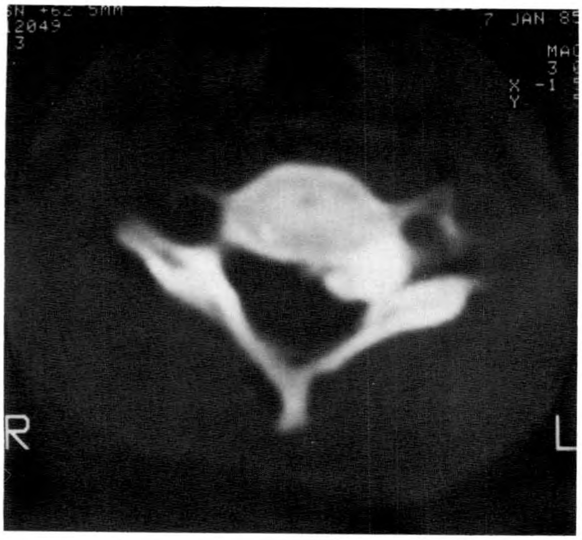
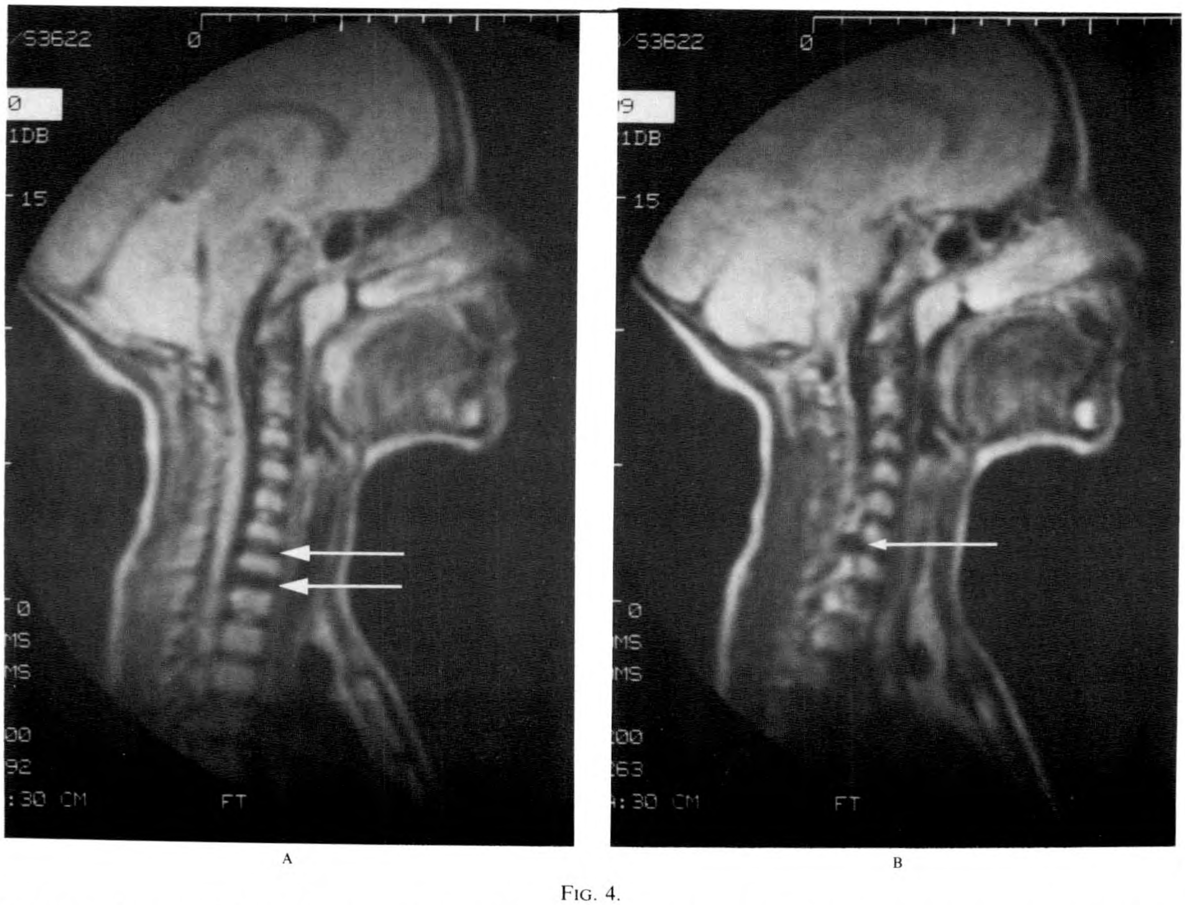


FIG. 3.

A CT scan (C6–C7 level) shows that a calcific fragment has herniated through a ruptured annulus fibrosus and occupies the left C6 neural foramen.



A

B

FIG. 4.

Two magnetic resonance images from a multisection T_2-weighted sequence (spin echo: TR = 3000 ms, TE = 60 ms). (A) Midline sagittal section. There is a diminished signal intensity from the C6–C7 and C7–T1 discs (arrows), and normal signal intensities from the remaining discs. (B) Para-sagittal section. There is a very low signal intensity in the position of the herniated fragment in the left C6 neural foramen (arrow).

1986, *The British Journal of Radiology*, *59*, 182–183

calcification is unknown but it is likely to be a condition distinct from the degenerative annulus fibrosus calcification seen in adults (Mainzer, 1973)

The childhood condition typically pursues a benign course with minimal symptoms and signs which resolve spontaneously, despite the rather alarming radiological findings This is so even in the presence of nucleus pulposus herniation, itself a rare "complication" of this uncommon entity (Mainzer, 1973).

Computed tomographic and MRI appearances in childhood disc calcification have not been reported previously and the findings on CT, in particular, emphasise the discrepancy between the clinical and the radiological features. Available experience suggests no necessity for surgical intervention

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Cutaneous seeding of pancreatic carcinoma by fine-needle aspiration biopsy

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Ultrasound-guided percutaneous fine-needle aspiration biopsy of the pancreas is a safe and accurate technique. We report the third case of cutaneous needle-track seeding of pancreatic carcinoma.

CASE REPORT

A 68-year-old woman presented in April 1984 with a 1-month history of obstructive jaundice, abdominal discomfort and weight loss Ultrasound examination showed a distended biliary tree above a 3 cm mass in the pancreatic head Fine-needle aspiration biopsy was performed using two passes with a 22-gauge needle. Cytology of the aspirated material showed normal ductal cells only. Two further attempts to obtain cytology were performed: in the first, five passes with a 22-gauge needle and a core biopsy with a 19-gauge Otto needle were made, in the second, three passes with a 22-gauge needle were made. In neither was there any evidence of malignancy A presumptive diagnosis of carcinoma of the pancreas was made and an 8-gauge biliary endoprosthesis was inserted endoscopically. Her jaundice quickly resolved

She presented again in October 1984 with a short history of gastric outlet obstruction. On examination she had a 1.1 cm × 0 7 cm cutaneous nodule in the epigastrium (Fig 1) Ultrasound and barium studies showed compression of the second part of the duodenum by a large tumour mass Laparotomy was performed; there were multiple peritoneal seedlings and a large tumour mass in the head of the pancreas. A choledochoduodenostomy and gastrojejunostomy were performed. Histology obtained from the pancreatic mass, a peritoneal deposit and the skin nodule showed poorly differentiated adenocarcinoma

DISCUSSION

Abdominal fine-needle aspiration biopsy has a remarkably low complication rate (Livraghi et al, 1983). Cutaneous seeding of carcinoma has been reported on two previous occasions (Ferrucci et al, 1979; Smith et al, 1980); both were from pancreatic carcinomas. In this case and that of Ferrucci et al, a large number of needle passes were performed on more than one day. No details are available from the report of Smith. In our patient a 19-gauge core-cutting needle was used once and this may have been responsible for seeding a large fragment of tumour. It is interesting that, despite the aggressive nature of this tumour, the cytology was repeatedly negative.

Experimental evidence on needle-track seeding is scanty. Animal studies using highly malignant tumours in genetically susceptible mice showed that fine-needle aspiration biopsy disseminated between 10^2 and 10^4 cells along the track and that this could result in implantation (Ryd et al, 1983). Autotransplantation of

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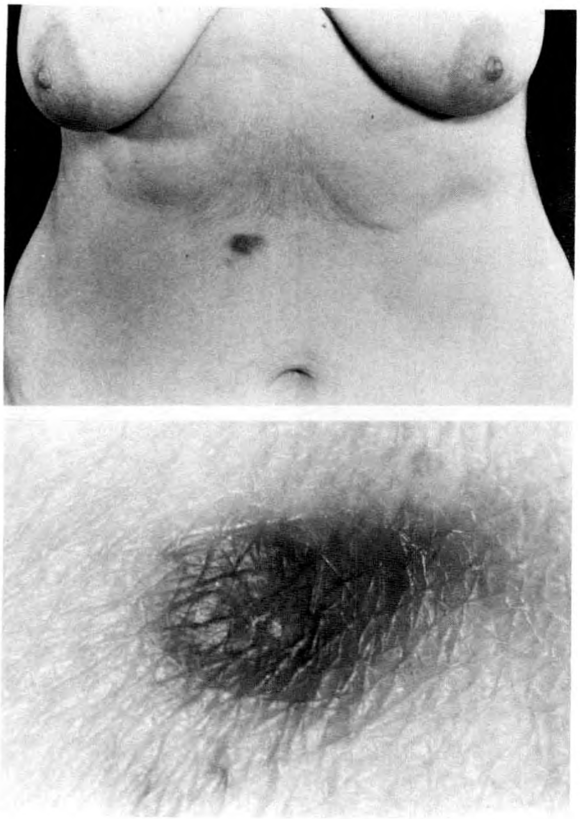

FIG. 1.

Cutaneous nodule in the epigastrium.

tumours has been performed in man and much larger inocula, of at least 10^6, have been required to achieve tumour growth (Southam & Brunschwig, 1961; Vaitkevicius et al, 1964).

The risk of needle-track implantation is very small and is probably related to the number of needle passes. This could be minimised by immediate microscopy of the aspirate, but resources for this are not widely available in the United Kingdom. The risk can probably be further reduced by limiting the use of core-cutting needles to cases where histology is needed and by using an outer-sheath needle to puncture the abdominal wall.

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Ultrasonography of hepatic portal venous gas due to diverticulitis

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Diverticulitis is an infrequent cause of hepatic portal venous gas (HPVG) and it is not associated with the grave prognosis of the more common HPVG due to infarcted bowel.

CASE REPORT

A 55-year-old man presented with a nine-day history of central and upper abdominal pain, rigors and anorexia. He had noticed mild jaundice for six days and had had one episode of blood-streaked faeces five days earlier. He was febrile and had generalised, slight abdominal tenderness, maximal in both upper quadrants.

Abdominal ultrasonography on the day of admission revealed a normal biliary tree and a few small hyperechoic foci in the region of the dome of the liver (Fig. 1). Two days later, repeat hepatic ultrasonography revealed diffuse multiple small hyperechoic foci which were interpreted as being gas in the biliary tree (Fig. 2). An abdominal radiograph confirmed the presence of the gas (Fig. 3). A barium meal, the following day, was normal and revealed no further evidence of gas in the liver and hepatic ultrasonography at this stage was also normal. An endoscopic retrograde cholangiopancreatogram identified normal pancreatic and bile ducts, but a barium enema showed an area of sigmoid diverticulitis and fistulation to both small and large intestines (Fig. 4). On reviewing the original abdominal

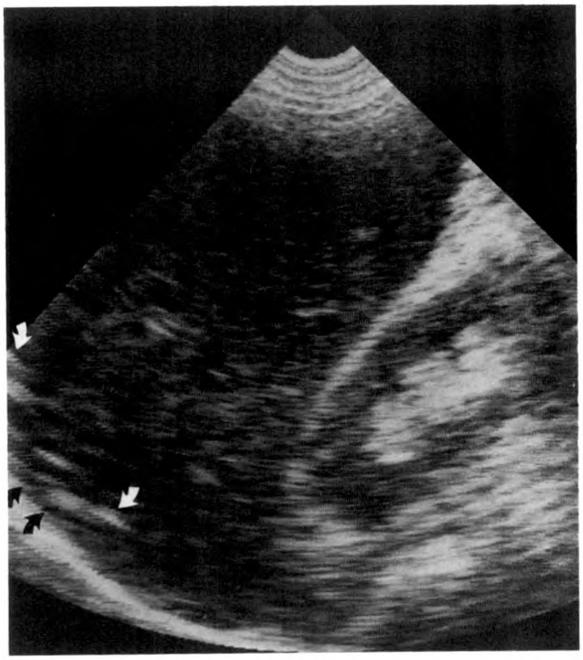

FIG. 1.

Sagittal ultrasonogram of right lobe of liver and kidney. Small hyperechoic foci (arrows) in liver periphery. Central liver is clear.

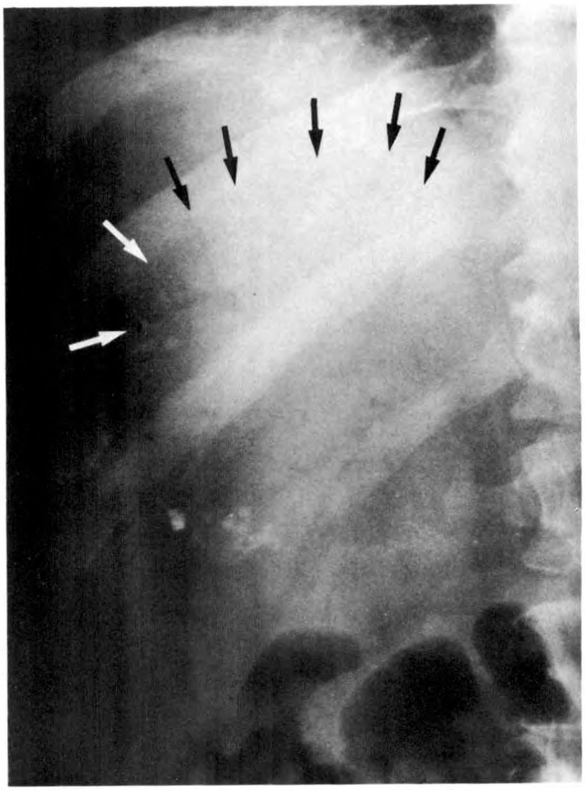

FIG. 3.

Abdominal radiograph. Branching translucencies due to gas in hepatic portal veins (arrows). The gas is well short of the liver's edge.

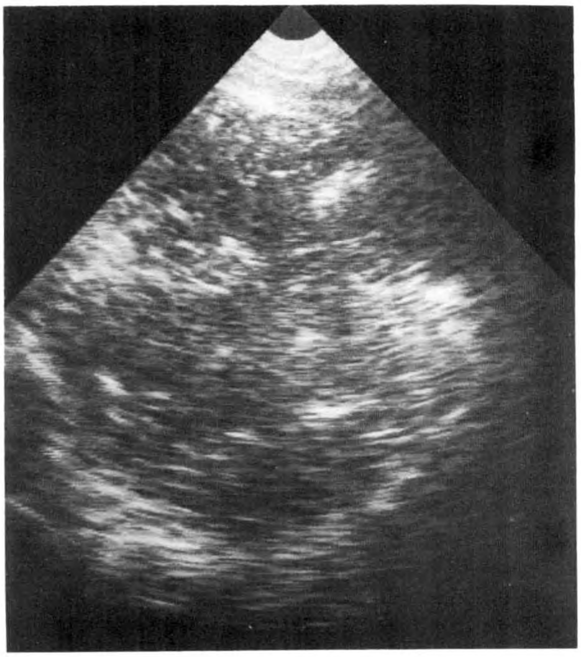

FIG. 2.

2 days later. Hyperechoic foci throughout the liver. The hepatic portal venous gas was misinterpreted as gas in biliary tree.

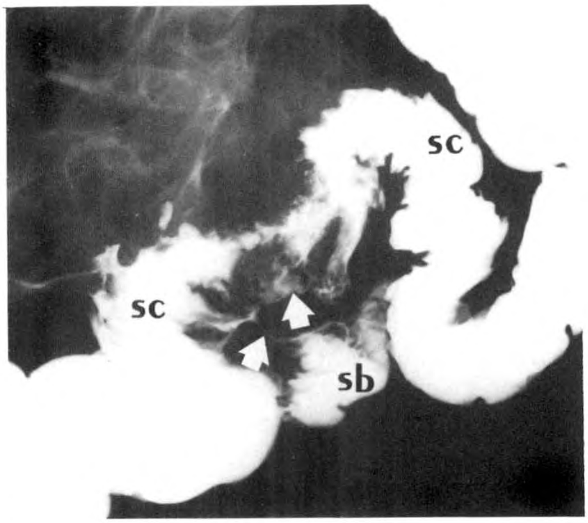

FIG. 4.

Barium enema. Area of sigmoid diverticulitis with fistulation (arrows) to small and large bowels. sc = sigmoid colon; sb = small bowel.

radiographs (Fig. 3), it was apparent that the gas seen was in hepatic portal veins

Throughout this period the patient improved slowly while on broad spectrum intravenous antibiotics. Initial blood cultures yielded *Proteus morganii, Escherischia coli* and *Bacteroides vulgatus* He settled completely and was discharged after four weeks The sigmoid diverticulitis and fistulation were confirmed surgically two months later

DISCUSSION

HPVG is a radiological finding associated most commonly with ischaemic, necrotic bowel (Liebman et al, 1978) In these cases the 90% mortality reflects the gravity of HPVG, the detection of which usually indicates the need for urgent laparotomy (Liebman et al, 1978; Traverso, 1981). A much lower mortality is associated with non-ischaemic causes of HPVG such as intra-abdominal sepsis, bowel distension, pancreatitis, gastric ulcer and diverticulitis (Liebman et al, 1978; Cambria & Margolies, 1982; Graham et al, 1975).

When small bright echoes, sometimes with acoustic shadowing, are identified in the liver during ultrasonography, an abdominal radiograph may confirm the presence of HPVG. HPVG has to be differentiated from biliary tree gas, the more common cause of a branching gas pattern overlying the liver. HPVG is more peripheral in its distribution and extends to within 2 cm of the liver's edge (Susman & Senturia, 1960; Sisk, 1961) On the earliest ultrasonogram (Fig. 1) the peripheral distribution of HPVG can be appreciated while the more central liver is clear The radiological confusion in our patient resulted from the inability to detect gas extending to the liver's edge (Fig. 3). The gas was present mainly in the anterior branches of the intrahepatic portal veins so that the many gas-filled branches were not seen extending out to the visualised edge of the liver shadow. Another characteristic feature of HPVG is its transience, as in our case (Traverso, 1981) When a large amount of gas is present, the radiological distinction of HPVG from biliary tree gas may be impossible as the gas will be located both centrally and peripherally (Gosink, 1981). Real-time scanning may detect moving bubbles in the main portal veins (Laing et al 1984, Merritt et al, 1984; Nachtegaele et al, 1982) and may be more sensitive than radiography in detecting portal venous gas (Merritt et al, 1984).

ACKNOWLEDGMENTS

The authors wish to thank Marie Ayling for the secretarial assistance and Darren Brown for the photography.

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Book review

Medical Effects of Ionizing Radiation. by F. A. Mettler and R. D. Moseley, pp. xi+288, 1985 (Grune & Stratton, Orlando, Florida)
ISBN 0–8089–1704–8

This book is described as a "source book" with an audience "... including physicians, nurses, health physicists, allied health professionals, and lawyers with a medico-legal background."! Data are almost entirely from human sources; radiotherapy, accidental or occupational exposures, and the survivors of the use of nuclear weapons at Hiroshima and Nagasaki.

An introductory chapter on basic radiation physics, chemistry and biology is remarkably clearly written, to the point where it would be a good initial point of contact for Part I F.R.C.R. candidates. Essentially, the biological section paraphrases Hall, and the section on radiation effects on cell and organ systems paraphrases Rubin and Casarett. A great deal of time is, however, spent on dose fractionation and the NSD/TDF system, complete with extensive reproduction of TDF tables, without adequate caveat on the limitations to their applicability. A section on sources of radiation exposure is again well written, but clearly slanted to the American population. Further sections cover effects on genetic material, cancer induction, and dose-response models, carcinogenesis in specific sites, direct (non-stochastic) effects of radiation and *in-utero* irradiation, and they are really quite extensively annotated bibliographies which even the regular practitioner in the field will find useful ("where *was* that reference on ...") A short chapter on plutonium, however, carries this to almost the *reductio ad absurdum* although concluding with the forthright statement "... the epidemiologic studies of plutonium in humans indicate that the risks are not substantially higher than can be calculated from current UNSCEAR and BEIR risk estimates." More contentious are the final chapters on probability of causation in an individual, and on perception and acceptance of risk which are inevitably more philosophical. The choice of three example cases on probability of causation in which the probability of radiation being the cause of the untoward effect is dismissively low is probably unwise if the book is to have an audience wider than "committed" radiation professionals! The discussion of acceptance of risks is inevitably superficial and the references are, remarkably, confined to the "pros" rather than the "antis".

Apart from the caveat that the quite clear type-face was a bit small for the middle-aged reader, the book is well produced and it carries a useful glossary and appendixes on radiation source terms and conversion of units. It is a very good effort, and will probably be found on the bookshelves of most professionals in the radiation protection business before long. Too few radiologists really concern themselves with radiation protection other than minimising the number of films taken and demanding of their staff that the equipment be in good condition. If they take *any* interest in the broader problems of radiation protection, this would be a useful single volume to have on their shelves as a starting point.

ROGER J. BERRY

1986, *The British Journal of Radiology*, 59, 187–188 FEBRUARY 1986

Case of the month

The case of the bulging Bulgarian

By Zamir Halpern, M.D., Mordechai Averbuch, M.D., Joseph Papo, M.D., Ruth Shilo, M.D. and Yoram Levo, M.D.

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(Received November 1984)

A 67-year-old Jewish male born in Bulgaria was admitted because of progressive swelling of the abdomen and both legs. The patient gave a history of recurrent orogenital ulceration, arthralgia and pustular dermatitis for the past 10 years. The relevant physical examination revealed severe oedema of both legs with trophic skin changes and ulcerating stasis dermatitis. He had marked distension of the superficial abdominal veins. There was no evidence of liver disease or ascites. Routine laboratory tests as well as barium examination of the gastrointestinal tract, a chest radiograph and a liver and spleen scan were all normal.

An ultrasound examination (Fig. 1) and a CT scan (Fig. 2) of the upper abdomen were performed and are illustrated.

What is the clinical diagnosis and what do the investigations show?

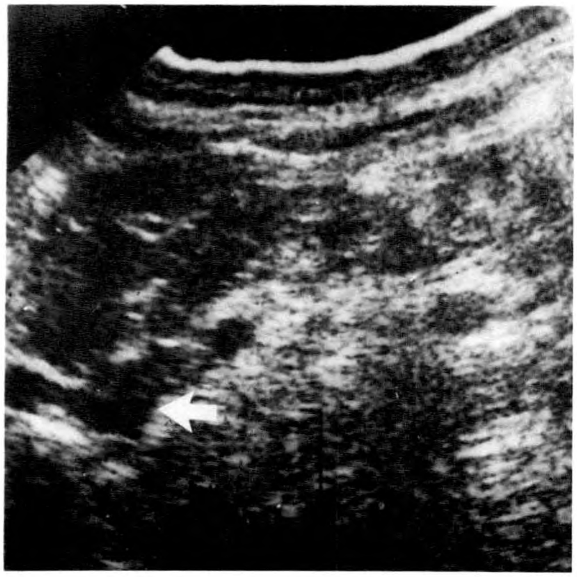

FIG. 1.

A longitudinal, right parasagittal abdominal scan in the region of the liver.

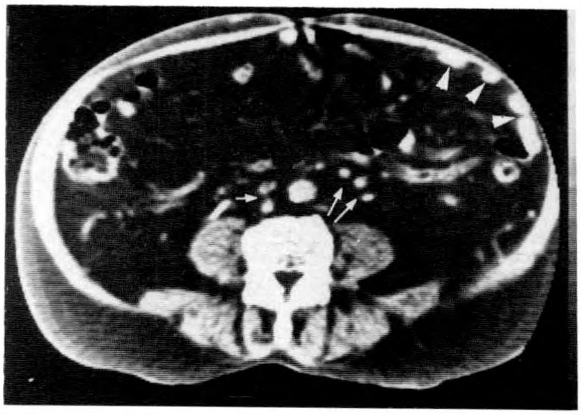

FIG. 2.

A transverse CT section adjacent to the lower pole of the kidneys.
(after intravenous contrast medium)

Since Behcet in 1937 described a triad of orogenital ulceration and ocular lesions, a number of additional features have been recognised as part of the complex now known as Behcet's syndrome (Chajek and Fainaru, 1975). These include erythema nodosum, pustular dermatitis, arthritis, neurological disorders and recurrent thrombophlebitis.

The ultrasound study clearly demonstrated complete obstruction of the inferior vena cava (IVC) (arrow) in the presence of a normal liver and spleen, and the absence of ascites. The CT scan shows the non-visualisation of the IVC and the superficial subcutaneous (arrow-heads) and deep peri-aortic and paravertebral venous network (long arrows) bypassing the occlusion.

Bilateral femoral venography (Fig. 3) showed the collateral venous pathways.

Vascular involvement such as recurrent superficial or deep thrombophlebitis is relatively common in Behcet's syndrome (Chajek and Fainaru, 1975). In contrast, obstruction of the inferior or superior vena cava is a rare manifestation of the disease, and only very few cases have been reported in recent years (Enoch et al, 1968; Kansu et al, 1972). The true incidence of caval thrombosis is yet to be determined. However, a relatively higher incidence among Jews has been suggested. Until recently the only way of documenting major vein occlusion was by venography. This procedure is obviously associated with all the possible complications of an invasive technique. In Behcet's syndrome the problems associated with venography are greatly increased because of the widespread nature of the vascular involvement. Moreover, the procedure might enhance vascular injury and thrombosis due to the particular vulnerability of the vascular system, and the increased coagulability which characterise Behcet's disease. The etiology and pathogenesis of this syndrome are as yet unknown, but the disease is associated with enhanced chemotaxis of leukocytes and inflammatory response and with decreased fibrinolytic activity (Chajek and Fainaru, 1975). It is well known that relatively severe skin lesions may follow a needle-puncture of the skin in Behcet's disease (the "pin-prick" sign).

In view of these possible risks of venography in Behcet's disease, the need for alternative, non-invasive, imaging techniques is apparent.

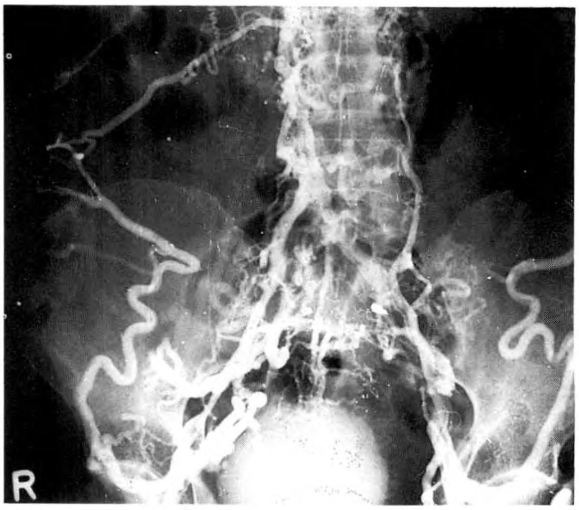

FIG. 3.

Bilateral venography showing both inguinal areas and abdomen. The IVC is not visualised, and dilated paravertebral and abdominal-wall venous collaterals are demonstrated.

In the patient presented herein, ultrasound and CT proved to be extremely useful and accurate in establishing the diagnosis of IVC occlusion. We believe that these techniques should replace venography in patients with the presumptive diagnosis of IVC obstruction, especially in Behcet's disease where invasive procedures are contraindicated. Some patients with IVC obstruction will develop the syndrome of hepatic venous hypertension (Budd-Chiari) in which ascites is usually present and which may be associated with Behcet's syndrome. In some of these patients and particularly in those having a web in the IVC, cavography and balloon dilatation may be helpful (Jeans et al, 1983).

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Short communications

Artefactual results with CHIP perhydrate

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(*Received July 1985*)

Several investigations using cis-dichloro-bis(isopropylamine) trans-dihydroxy platinum IV (CHIP) have been carried out in our laboratory (Nias & Szumiel, 1977; Nias et al, 1979, Laverick & Nias, 1981a, b; Bales et al, 1982; Nias et al, 1982; Bocian et al, 1983a, b, Barot et al, 1985) Initially, the compound had been synthesised containing 1 mole equivalent of hydrogen peroxide for 2 moles of CHIP. The anhydrous form of CHIP is now available and under clinical trial.

We have compared the toxicity of CHIP perhydrate and anhydrous CHIP on exponentially growing Chinese hamster ovary (CHO) cells cultured in monolayer with minimum essential medium (MEM) plus 15% foetal calf serum (FCS) The cells were treated with varying concentrations of drug for 1 h at 37°C, then trypsinised and plated out for colony-forming ability Figure 1 shows there is a very substantial difference in the toxicity of the two drug preparations (CHIP perhydrate $D_0 = 87$ µM; anhydrous, $D_0 = 200$ µM)

Catalase is an enzyme capable of degrading hydrogen peroxide to oxygen and water, and if present in the medium the CHIP perhydrate response shifts to that of the anhydrous CHIP (Fig 1) This indicates that once CHIP perhydrate is in solution, hydrogen peroxide, which is toxic towards cells unless broken down, is released.

Early work using CHIP perhydrate showed that the degree of toxicity was dependent upon whether the choice of culture medium was Ham's F12 or MEM (Laverick & Nias, 1981b; Barot et al, 1985) The CHIP perhydrate was shown to be much less toxic in Ham's F12 compared to MEM, and the authors had ascribed this difference to CHIP reacting with cysteine which is present in Ham's F12 at a concentration of 30 µg/ml We have repeated this work using anhydrous CHIP and found that although the drug is less toxic in Ham's F12, the difference between the two media is much less dramatic. The previous results were most likely demonstrating the protective action of cysteine in the Ham's F12 medium against the peroxide component of CHIP perhydrate In MEM, however, the hydrogen peroxide was responsible for much of the prevailing toxicity and, therefore, effects previously observed with CHIP perhydrate may have been attributable to the peroxide

It is of note that the work of Mong et al (1982), demonstrating DNA strand breakage by CHIP, was later disproved by Vollano et al (1984) who showed that it was lattice hydrogen peroxide, and not CHIP, which cleaved DNA

Many of the previous experiments investigating CHIP perhydrate on the radiation response of CHO cells have since been repeated with anhydrous CHIP using similar experimental protocols The results do not confirm either oxic or hypoxic radiosensitisation by CHIP as previously reported

CHIP perhydrate is an unusual formulation of a platinum coordination complex which appeared to be an effective hypoxic cell radiosensitiser *in vitro*, but the biological and radiobiological effects of anhydrous CHIP are those which are important *in vivo* and in clinical practice.

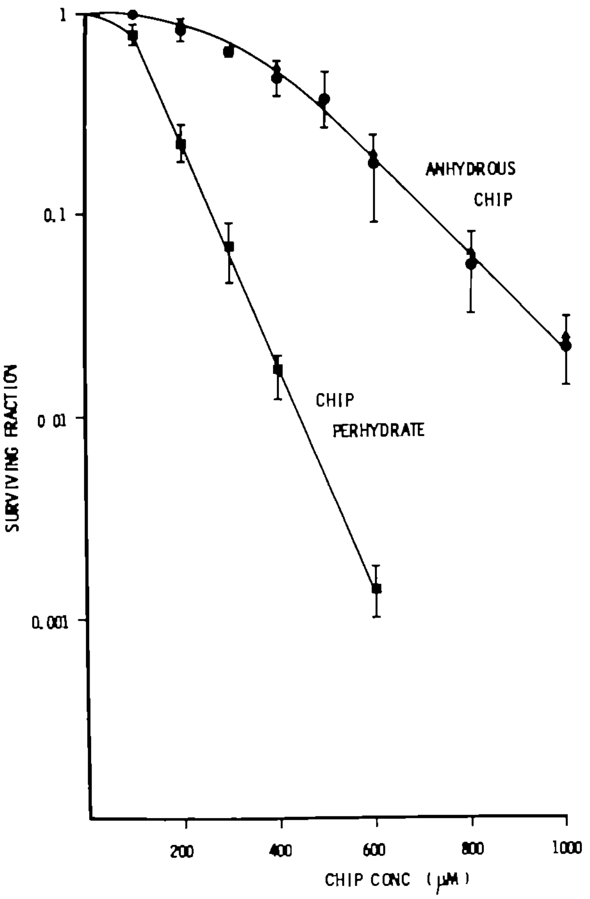

FIG 1

Survival of CHO cells cultured in MEM plus 15% FCS after drug treatment for 1 h at 37°C with CHIP perhydrate (■) (error bars represent range of data from three experiments), CHIP perhydrate in the presence of 100 µg/ml catalase (▲) (data points represent the mean of two experiments where the range does not exceed that of anhydrous CHIP), anhydrous CHIP (●) (error bars indicate the standard deviation from at least six experiments)

Work is in progress to investigate a possible interaction with anhydrous CHIP and radiation at much higher drug concentrations.

ACKNOWLEDGMENTS

Kind thanks to Johnson Matthey for the supply of CHIP perhydrate and to Bristol-Myers for the supply of anhydrous CHIP. This work was supported by the Cancer Research Campaign.

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A preliminary study of the possible benefits of using carbon dioxide insufflation during double-contrast barium enema

By D. S. Grant, B.Sc., M.B.Ch.B., M.R.C.P., *C. I. Bartram, F.R.C.R., F.R.C.P. and †C. W. Heron, M.R.C.P., F.R.C.R.

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(*Received July 1985*)

Routine examinations such as the double-contrast barium enema (DCBE) should be designed to cause the minimal discomfort possible without compromising the quality of the study. It has been suggested that carbon dioxide for insufflation, instead of air, reduces the discomfort experienced by patients after DCBE (Levene & Kaufman, 1957; Pochaczevsky & Sherman, 1963, Scott-Harden et al, 1967).

Carbon dioxide is absorbed from the bowel 150 times faster than the nitrogen in air, and is promptly eliminated via the lungs. The bowel should therefore deflate more rapidly when carbon dioxide is used instead of air, so that one would expect distension and cramps to be reduced in intensity and to disappear more quickly after the examination.

To investigate the symptomatic benefit of using carbon dioxide and to relate this to the gas remaining in the bowel, patients undergoing DCBE were allocated randomly into two groups of 25 each. No selection was made as to age or sex, but patients with previous surgery or with known serious disease were excluded from the study. Each received the department's standard bowel preparation, which includes a cleansing water enema. An IV injection of 20 mg of hyoscine butylbromide was given at the beginning of the DCBE. Sufficient gas was introduced to achieve adequate visualisation of the colon (as estimated by the same single observer (D.S.G.) to avoid

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TABLE I

	Patients' reponse						Gas on delayed AE film			
	Distension			Cramps			Colonic grade			Small bowel present
	None	Mild	Severe	None	Mild	Severe	0	1	2	
Air	10	14	1	12	12	1	0	4	21	15
Carbon dioxide	12	13	0	20	5	0	2	14	9	8

interpersonal variation) The air or carbon dioxide was administered via an inflated plastic bag, so that there was no difference in technique

Thirty minutes after leaving the lavatory, having evacuated as much of the barium and gas as possible, the patients were asked to complete a short questionnaire. Three possible responses (none, mild, or severe) could be made to two questions "Do you now have any abdominal distension?", and "Are you now suffering from abnormal cramps?"

A supine film of the abdomen was taken also, and the residual bowel gas assessed by one radiologist (D S.G.) In the small bowel, gas was noted as either present or absent, but an estimate was made of the gas remaining in the large bowel, in the following way (since actual volumetric analysis proved difficult). The colon was subdivided into three segments. ascending colon and hepatic flexure, transverse colon and splenic flexure, descending colon and sigmoid colon The presence of significant residual gas was recorded in each segment, and an overall grading given:

Grade 0—less than one segment gas-filled
Grade 1—one or two segments gas-filled
Grade 2—three segments gas-filled.

Only one patient who had air insufflation complained of severe distension. The remainder considered they had either only mild distension or none. The same was true for abdominal cramps No significant difference between carbon dioxide and air was found between either group on chi-squared testing No patient had either severe abdominal distension or cramps when carbon dioxide was used

The delayed post-evacuation film showed that with air more gas was retained in the colon and a higher proportion of gas remained in the small bowel, than with carbon dioxide, but the differences were not statistically significant No correlation was apparent between the retention of gas and symptoms.

The timing of the questionnaire and film were dictated by expedience, as it was felt that 30 minutes was the maximum that patients could reasonably be asked to wait after the examination was finished. This period may be criticised as being too short, although Hussein et al (1984), using the same time interval, were able to detect a significant advantage for carbon dioxide following colonoscopy. A possible explanation for the difference is that at the end of colonoscopy, considerable volumes of gas were sucked out before the endoscope was withdrawn The relatively smaller volumes remaining may then disappear completely within this period Moreover, Pochaczevsky & Sherman (1963) noted a significant reduction in discomfort using carbon dioxide, and in no instance did this last for more than half an hour

It must be concluded that severe discomfort after DCBE is an idiosyncratic response, and no direct correlation has been shown between symptoms and the volume of gas remaining in the colon or small bowel In individual cases discomfort may be ameliorated by using carbon dioxide, which is more rapidly absorbed from the gastrointestinal tract However, this study has not suggested that this will be of general benefit. Considering the technical difficulties involved in using carbon dioxide for insufflation, it does not appear to be a worthwhile modification to the examination

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Book review

Radiation Protection in Hospitals By R. F. Mould, pp 210 + index, 1985 (Adam Hilger Ltd, Bristol), £19.50
ISBN 0-85274-802-7

This book has been written to cater for readers from differing hospital environments and aims "to instil universal principles of good radiation practice into the reader". It has evolved from Dr Mould's lecturing in many countries and NRCP, WHO and NRPB documents are extensively quoted. These lengthy inserts make the text difficult to follow at times.

In view of the recent publication of the *Ionising Radiations Regulations 1985*, a contemporary book on radiation protection would be particularly timely for the UK reader. Frequent reference to the 1983 NRPB Consultative Document *Draft Guidance Notes for the Protection of Persons against Ionising Radiation Arising from Medical and Dental Use* in this volume is unfortunate since the draft legislation on which the document was based has undergone considerable revision. For example the eye dose limit for adult employees is now 150 mSv, not the 300 mSv quoted

The first part of the book contains basic radiation physics that lays the foundations for the practicalities of radiation protection. Although this is intended to be an elementary text, it may not be easy for the general hospital employee to follow.

Part II of the book covers, in six chapters, areas in hospitals where radiation is present. Some of these chapters are muddled, for example information on nuclear medicine diagnostics is included in the chapter on ^{131}I therapy, whereas protection requirements for therapeutic doses of other unsealed radionuclides are omitted In the diagnostic radiology chapter, KeV and kVp have been confused.

The book is extensively illustrated, but the wide use of historic photographs, although interesting, does not, in general, contribute to the book's stated aim.

A useful collection of available guidance is provided by this book but the basic "dos and don'ts" of good radiation practice are not sufficiently clearly emphasised to justify the expenditure of £19 50

K PALMER

1986, *The British Journal of Radiology*, 59, 193–194 FEBRUARY 1986

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

Agreement of quadratic and CRE models in predicting the late effects of continuous low dose-rate radiotherapy

THE EDITOR—SIR,

It has been known for some time, and is now generally accepted, that normal tissue isoeffect formulae based on the Ellis equation (Ellis, 1969) including the CRE and TDF formulations do not correctly account for the late-occurring effects of fractionated radiotherapy (Bates & Peters, 1975; Singh, 1978; Turesson, 1978). Correction factors have been proposed (Turesson & Notter, 1979) to take account of the increased effect on late-responding tissues of large fractions but this approach is both unwieldy and unsatisfactory from a philosophical point of view. Alternatively, the exponents in these power function models may be varied depending on the tissue in question (Wara et al, 1973; Pezner & Archambeau 1981). Currently, the favoured model for fractionated radiotherapy is the linear quadratic (Barendsen, 1982; Thames et al, 1982, Fowler, 1984). In this approach, organ-specific parameters known as α/β ratios can be used in the calculation of isoeffective schedules for the specified tissues. When α/β ratios commensurate with acutely responding tissues are used, the linear quadratic model predictions are close to those of the CRE or TDF equations for radiotherapy schedules of similar duration, whereas α/β ratios descriptive of late effects lead to predictions which are substantially different from the CRE or TDP formulae.

Recently, the linear quadratic model has been extended to include continuous low dose-rate radiotherapy with constant or decaying sources (Dale, 1985). Here it is convenient to use a quantity called the extrapolated response dose (ERD). This may be thought of as the dose required for a particular biological effect if treatment is given as an infinitely large number of infinitesimally small doses. The total dose (TD) is related to the ERD and a quantity called the relative effectiveness (RE) by

$$\mathrm{ERD} = \mathrm{RE} \times \mathrm{TD} \qquad (1)$$

For continuous irradiation, the RE is dependent on the α/β ratio, the dose-rate, the irradiation time and the repair kinetics characterised by the time constant of the process of repair of radiation damage.

Two radiotherapy schedules, A and B, are isoeffective if their ERDs are equal, *i.e.* if

$$\mathrm{TD}_A \times \mathrm{RE}_A = \mathrm{TD}_B \times \mathrm{RE}_B \qquad (2)$$

If, for example, we choose Schedule A to be 6000 cGy in 7 days, we can choose a different irradiation time for Schedule B and, using Dale's equation (denoted by D in his paper), calculate the dose which is required for the two schedules to be isoeffective. By varying the irradiation time of Schedule B, a curve of isoeffective dose as a function of irradiation time can be produced. The shape of the curve will depend on the α/β ratio and also on the time constant for repair. If $T_{\frac{1}{2}}$ is the half-time for repair of radiation damage we may take estimates of 1.5 h and 1.0 h for late and acutely responding tissues respectively (Thames et al, 1984). If we also take representative α/β ratios: $\alpha/\beta = 300$ cGy for late effects, $\alpha/\beta = 1000$ cGy for acute effects (Fowler, 1984), then we may expect that the resulting curves will be valid for late and acute responses, respectively, if the model is an adequate description. These curves are shown in Fig. 1 together with the isoeffective dose curve produced by the combined clinical data of Paterson and Green upon which the CRE scale for continuous low dose-rate irradiation schedules is based (Kirk et al, 1972). It can be clearly seen that the "late effects" and CRE curves correspond closely, whilst the "acute effects" and CRE curves are in obvious disagreement.

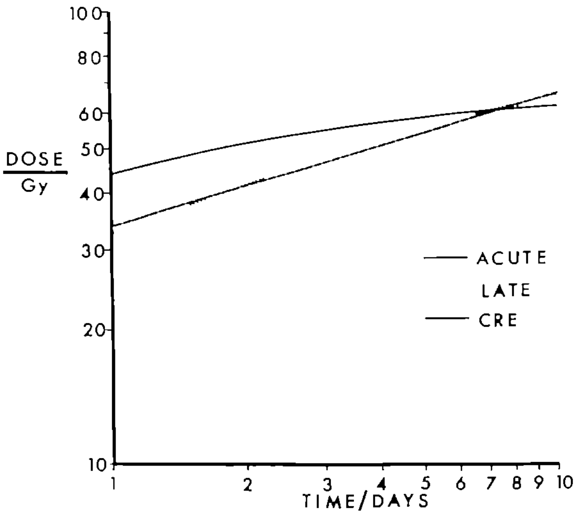

FIG 1

The equivalence of the CRE and quadratic models for late effects.

It is worthwhile to point out that the fractionated and continuous CRE equations should not be put into the same category. For continuous low dose-rate radiotherapy, the CRE and the late effects quadratic model are in agreement.

Yours, etc.,

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(*Received September 1985*)

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(*Author's reply*)

THE EDITOR—SIR,

Dr O'Donoghue's letter highlights once again the inherent difficulties associated with the NSD/TDF/CRE formulations According to the originator of the NSD formula (Ellis, 1980): "the NSD concept, from which the CRE system is developed . aimed to provide a one-figure estimate in rets, based on deductive and inductive reasoning, of the *late effects* of normal connective tissue" (my italics) In extending the CRE concept to protracted radiotherapy, Kirk et al (1972) used the clinical data of Paterson and Green, which are also said to relate to connective tissue tolerance. It would, therefore, seem reasonable to expect the isoeffect values of Paterson and Green for continuous low dose-rate irradiation to agree with linear-quadratic (LQ) predictions based on a low α/β ratio, (see Dr. O'Donoghue's graph). However, it must be stated that there are doubts about the reliability of the clinical data used by Kirk et al. The results of Green were only available in a personal communication to Ellis (1968), and Paterson's data were originally presented (Paterson, 1952) in a very simplistic form. It may be wrong, therefore, to read too much into the apparent agreement between these sets of data and late-reaction LQ predictions

If isoeffect curves for daily irradiation, based on a fractionated regime delivering 60 Gy/30 fractions, are derived from both the NSD and LQ formulae, it is clear that the NSD predictions agree much more with LQ values based on $\alpha/\beta = 2$–3 Gy than with $\alpha/\beta = 10$ Gy. In making this particular comparison, we are essentially saying that, in the Ellis equation, total dose is approximately proportional to $N^{0.35}$. Therefore, the NSD equation, when applied to five fractions per week schedules, does indeed appear to be correct for late-reacting effects If a similar comparison is now made for cases where the overall time is kept constant, *i.e.* where the Ellis equation gives total doses proportional to $N^{0.24}$, the NSD values are much closer to LQ values with $\alpha/\beta = 10$ Gy. Therefore, in general usage, the Ellis formula can be expected to behave as though it is describing any one of a variety of radiation effects; the particular equivalent α/β value will depend on the specific fractionation details This has been demonstrated clinically by Turesson and Notter (1984a).

When the results of Bates and Peters (1975) are examined, it is found that the NSD prediction (that 5350 R/12 fractions at three fractions/week is equivalent to 4315 R/six fractions at two fractions/week) correspond to an α/β ratio of ~ 7 Gy. Thus, the NSD equation, which is compatible with low α/β values when five fractions per week regimes are compared, is more compatible with $\alpha/\beta = 7$ Gy where these particular three fractions/week and two fractions/week schedules are compared The clinical findings of Singh (1978), who changed from five fractions/week to one fraction/week when treating Stage III carcinoma of the cervix, are also due to a similar problem associated with the TDF formula. In this case the TDF predictions for the required dose reductions correspond to $\alpha/\beta \sim 8$ Gy.

The foundations of the basic NSD equation (and hence TDF and CRE also) have been criticised by a number of authors (*e g.* Liversage, 1971) and the exponentially based time factors are clearly inappropriate (Fowler, 1984). The fractionated LQ model itself suffers from the potential disadvantage that it says nothing at all about overall time factors (Fowler, 1984, Dale, 1985), but this may not be of major significance in many cases as it now appears that acute damage repair may be initially delayed, and then followed by accelerated proliferation (*e g.* Turesson & Notter, 1984a,b). Also, although it is not always possible to know which α/β value to use in a particular clinical case, the fact that the parameter always appears in LQ equations serves as a reminder that users need to consider carefully the types of radiation effects which are to be matched This is not possible with the traditional models for fractionated radiotherapy and, consequently, there have been reports of clinical problems

Yours, etc,
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(*Received September 1985*)

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A randomised comparison of photons and 15 MeV neutrons for the treatment of carcinoma of the bladder

THE EDITOR—SIR,

The reader of the paper by Pointon et al (1985) might well infer from the discussion section that the Hammersmith trials included carcinoma of the bladder. In fact, we have treated no patients with bladder cancer because the penetration of our neutron beam was inadequate and its penumbra too wide. The beam of 15 MeV neutrons used by Dr. Pointon had similar penetration and an even worse penumbra. In addition, we had the problem of a beam fixed in a horizontal direction.

Figure 2 and 3 of their paper show that the dose distributions with 15 MeV neutrons were markedly inferior to those obtained with 8 MV X rays which were used in the control arm. Perhaps it is not surprising that there was more morbidity after neutrons. To match the neutron dose distributions it would have been necessary to use a non-standard photon beam such as ^{60}Co gamma rays at 50 cm SSD. This manoeuvre was used by Wood et al (1950) for a comparison of X rays with radium gamma rays but would hardly be ethical today.

In the circumstances it is interesting that the recurrence rate with neutrons (38%) was lower than with photons (54%), albeit not to a statistically significant degree. We await with interest the results of trials of neutron therapy at Clatterbridge where the neutron beam will be more nearly equivalent to beams of megavoltage X rays.

Yours, etc.,
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(Received August 1985)

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Instability of radiation protection quantities

THE EDITOR—SIR,

I recently wrote a brief critique of the quantities used in radiation protection (Greening, 1984). I pointed out, in particular, that dose equivalent and effective dose equivalent were potentially unstable quantities as their definitions (*e.g.*, $H = D \times Q \times N$) included humanly judged factors such as Q, N and w_T that could well change with time. I hardly expected that instability to be demonstrated within a few months by the ICRP. However, the statement from the March 1985 meeting of the ICRP (ICRP, 1985) recommends that Q for fast neutrons should be doubled. This changes the *quantity* dose equivalent and, with it, the quantity effective dose equivalent, but the new quantities are to have the same names as the old quantities!

It is as if there had been a recommendation to limit the size of circles by saying that the *radius* should not exceed 5 cm, and when that recommended size was thought to be too large by a factor of two, saying that in future the *diameter* should not exceed 5 cm but that henceforth the diameter should be called the radius. Are you confused? If so, imagine the confusion of radiation users in future. How do you add up radiation doses over a period or compare doses at different dates when the quantities involved change in that period but the names do not?

It is surely necessary that radiation "doses" are expressed in terms of stable quantities. If it is thought desirable to change the amount of radiation received by workers or public it should be done by changing the number of *units* of the "dose" quantity, not by changing the *quantity* itself (without changing its name).

I will not pretend that there are no problems in resolving this issue, but the sooner radiation dose limitation is built on rock rather than on shifting sands, the better.

Yours, etc.,
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(Received September 1985)

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Spread of a testicular tumour to the contralateral groin: another case

THE EDITOR—SIR,

Alcock et al (1985) reported two cases of inguinal adenopathy as a presenting feature of a testicular tumour, one of these in the contralateral nodes Another case of presumed spread in the contralateral inguinal nodes is described here

A patient aged 36 years presented in April 1985 with a red and painful swelling (12 cm by 12 cm) of the left groin, swelling of the leg and pain in walking A right-sided inguinal hernia had been operatively repaired 18 years previously, and a left-sided one 10 years previously A biopsy of the groin tumour delivered the diagnosis of a metastasis of a seminoma. The consultant urologist found the testis on the left side unsuspect, but found a nodular testis enlarged by one-and-a-half times on the right side. A right-sided orchidectomy was performed, and a seminoma with capsular infiltration confirmed. A single involved inguinal node on the right side was detected. A biopsy of the clinically unsuspect left side seemed inadvisable because of a rapidly developing fungating ulcer in the left groin after the biopsy and the potential involvement of the left scrotum in a planned radiation field. It was therefore decided to give radiotherapy to the lymphatic region (inguinal, iliac and para-aortic nodes) and both scrota with 30 Gy to the whole target and 50 Gy total to the heavily involved left groin This resulted in a complete regression of the tumour and consequent wound-healing.

Although a second primary in the left testis on the side of the clinical lymphadenopathy cannot be completely excluded, a contralateral spread is quite probable. The reason is, as in the other reported case, a disturbed lymphatic system after bilateral inguinal surgery.

Yours, etc.,
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(*Received September 1985*)

REFERENCE

ALCOCK, C J, LAING, A. H & HUDDY, P., 1985. Inguinal lymphadenopathy as presenting feature in two cases of testicular tumor. *British Journal of Radiology*, *58*, 181–182.

Book received

The Editors acknowledge with thanks receipt of the following book, which has been placed in the Library of the British Institute of Radiology for use of members.

Graphical Representation of K-Shell and Total Internal Conversion Coefficients. From Z = 30–104. By J. D Cole, W. Lourens, J. H. Hamilton and B Van Nooijen, pp. 152, 1984 (Delft University Press), D fl. 75 ISBN 90 6275 158–X.

1985 Curt Westman Scholarship

The main reason for my trip to Sweden in May 1985 was to visit various radiology departments in several of the larger medical centres. I was hoping to see how the Swedes practise and teach general radiology and I was also particularly interested in their approach to vascular and interventional work The first half of my visit was spent in the old, historic city of Lund, southern Sweden There, the Radiology Department occupies three floors of a large multi-storey building, erected during the 1960s, the hospital has 1600 beds and serves as a regional centre for the south west of Sweden (population 1 5 million) By remaining in one department I was able to appreciate more of the "typical" aspects of Swedish radiology and, during the second half of my stay, visits to other departments in other cities showed this to be a fair representation The second half of my visit was based in Stockholm and comprised visits to various departments at the Karolinska and other teaching hospitals in Stockholm, combined with a visit to Uppsala

I shall try to cover fields which, I hope, will be of general interest as well as of particular personal interest

The working day

This invariably begins with a review of the previous day's work The radiological round begins at about 7.00–7.30 a m with presentations of all cases by a junior member of the radiology staff To facilitate this, clerical staff carefully load viewing alternators, the previous films etc having been made available. (The logistics of this, taking Lund hospital as an example, mean that, of 19 full-time clerks employed within the X-ray Department, three or four were solely engaged in preparing films for, or filing films after this meeting) The Radiological round lasts for about 20 minutes after which there is a Clinico-radiological round This description applies to Lund, in other departments the two rounds were combined Each clinical specialty has its own daily round. In Lund these occur simultaneously and as a result the 10 conference rooms within the X-ray Department are used for the meetings

Departmental work begins at about 8 00 a m and continues until 4 30–5 00 p m (with 1 hour 15 minutes lunch break) All departments provide a duty radiologist for cover outside normal hours who is compensated by extra payment (not popular due to the high rates of income tax), or by time off in lieu (very popular with most radiologists)

Staffing

There are approximately 600 radiologists in Sweden, a country with a population of some 8 million. In the United Kingdom there are approximately 900 radiologists serving a population of 56 million Thus the radiologist to population ratio is approximately 4 5 times higher in Sweden than in the UK It is also interesting to look at potential future implications A prime example is in the role of mammography and screening Several Swedish radiologists to whom I spoke, believe that in order to provide a full and adequate screening service for their female population, a realistic figure of 50 full-time extra radiologists will be required Simple extrapolation would suggest that some 350 extra radiologists would be needed in the UK to provide a similar and, presumably, adequate service.

Increased staffing levels among radiologists does, of course, demand higher secretarial, clerical, radiographic and auxillary staff numbers.

Radiological training

Basic undergraduate medical training in Sweden appears broadly similar to that in the UK, although during the years as a medical student the individual receives somewhere between 60 and 80 hours radiological teaching Newly qualified doctors spend two years as "interns" and are then able to choose a specialist career Radiological training lasts 5 years with a 6 month provision for research There is no formal examination in radiology as we have and the result appears to be a proficient, practical radiologist with active research interests Some senior Swedish radiologists feel that their juniors do not read enough general radiological texts and journals and that as a result they are producing radiologists with an inadequate depth of knowledge They regard our F R C R. examination as a wonderful way of encouraging further reading and whilst there does seem to be some merit in this philosophy, I am sure that there are Senior Radiologists to be found in the UK who feel the same way about their juniors, with or without the F.R C R examination.

After five years training, a radiologist is accredited and becomes a specialist. Unlike our Consultant grade, specialists in Sweden are often supervised in larger centres by their section leaders and heads of departments.

Research

In general terms, radiologists in Sweden are more active in research and publication. The facility for research is greater, this is made possible by more generous staffing levels making people available to do research, and this is also helped by the general role and position of the radiologist. In Sweden the radiologist's time is considered to be very valuable, for example a patient having angiography will be fully prepared for the examination and only then will the radiologist be called. The radiologist can then gown-up and proceed immediately with the local anaesthetic/arterial puncture.

The contributions to the medical literature indicate the success of this philosophy.

Swedish radiologists on the whole find it remarkable that the British are able to contribute so much to the literature, considering their pressure of work and limited resources. As one person succinctly put it "The English live on their brains".

As I outlined earlier, my personal interests include vascular and interventional work. It was this interest which really prompted the visit to Scandinavia where angiography has always been prominent.

During my two weeks in Lund, I saw six hepatic angiograms, three patients had ileal carcinoid with symptomatic hepatic metastases and were being treated by selective hepatic angiography followed by gelfoam embolisation. The procedure is repeated at intervals. The remaining three angiograms were purely diagnostic. Another patient, presenting with hypersplenism and varices secondary to splenic vein thrombosis was being treated by serial segmental splenic artery embolisation, again using gelfoam.

Obviously the type of angiography performed reflects, in part, the interests of the individual workers and the hospital staff itself. Nevertheless, the numbers and types of angiograms do reflect the greater role of angiography in Sweden. As well as alimentary tract, there were regular renal, femoral and upper limb angiograms. It was interesting to note the widespread practice of shaping one's own catheter and even shaping and bending guide wires. Whilst this may seem unnecessary in a lot of instances, it can be very effective at times, and the skill obviously takes some practice. It was interesting to note that in Lund, the radiologist seldom scrubs prior to angiography. Instead gloves are changed regularly as a means to prevent infection. Elsewhere a more traditional approach to sterile aseptic techniques was the norm.

Several of the departments I visited were using subtraction angiography, for example in the investigation of suspected renal artery stenosis.

Percutaneous transluminal angioplasty has not been accepted in Sweden as widely as in the UK. Certainly most of the larger centres were performing coronary angioplasty and its use in renal transplant arterial stenoses or occlusion was accepted, but very few centres did much peripheral angioplasty. For a country where the radiologist traditionally has a central and dominant role in medical practice, the ability to prise suitable patients from the surgeon was manifestly absent.

Other areas of interventional radiology have flourished in Sweden. There were varied approaches to renal stones and their removal. In all centres the percutaneous route was the chosen route. In Lund, Dr Leif Ekelund uses a balloon catheter to dilate a nephrostomy tract and works in conjunction with a urologist who performs nephroscopic removal of the stone with or without lithotripsy (Ekelund & Lindstedt, 1985). This technique is simple, safe and elegant but rather expensive since the cost of each disposable balloon catheter is approximately £180. In Stockholm one of the pioneers of percutaneous renal stone extraction, Dr I Fernstrom, and his staff use serial telescopic steel dilators for the nephrostomy and then remove the stone with a steerable catheter and Dormia basket (Fernstrom, 1983). Whichever the chosen technique, the role of stone extraction is firmly established.

Acknowledgments

I would like to thank Dr Curt Westman and the British Institute of Radiology for providing me with the opportunity of visiting Sweden and for the opportunity to meet and spend time with many eminent radiologists. The visit was very well organised and the hospitality extremely generous throughout, I could certainly recommend it as a worthwhile experience.

I would like to thank Drs Anders Lunderquist and Leif Ekelund for looking after me while in Lund, Drs Arvidsson, Ahlback and Hindmarsh in Stockholm and Dr Lorelius in Uppsala.

I would like to thank Dr Curt Westman, especially, for his kindness, hospitality and generosity which made the visit so enjoyable. I would also like to express thanks for the financial assistance provided by Dr Westman, the European Association of Radiology Education Trust Fund, the British Institute of Radiology and also the Plymouth Health Authority.

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Dr A P Wolinski,
Senior Registrar,
Plymouth General Hospital

Electromedical equipment safety testing for Europe

The growing emphasis on safety standards in Europe together with the harmonisation of IEC 601-1 and the EC Directive has led to increased pressure on manufacturers to demonstrate compliance with the requirements. In some countries, including West Germany, testing will soon be mandatory for certain types of apparatus.

To satisfy the needs of both nations, BSI Testing Services and TUV (Bayern) have agreed to co-operate, and the BSI Electromedical Laboratory is now able to offer a service of joint testing for both the UK and West Germany, leading to the award of a Certificate from BSI and the GS Mark from TUV.

For further information, please contact Mr J. Hartley, Head of Electromedical Section, BSI Testing Services, Maylands Avenue, Hemel Hempstead, Herts HP2 4SQ (Tel. 0442-3111).

The Radiological Research Trust

Trustees: J A Powell, D Phil, C Eng, F I E E., F R S E, W M Ross, T D, D L, M D, F R C S, F R.C R and P N T Wells, D Sc, F Eng

On November 1, 1985, this new Trust was born We hope that it grows up quickly, to help some of those who want support for their radiological research and now find it very difficult to obtain financial backing.

As yet it only owns pennies, but we are working to have it endowed.

Another way in which the Radiological Research Trust may help, apart from direct funding, is by giving its recommendations on behalf of project applicants to other grant-giving bodies Our Trust will soon have a Panel of expert advisors who will assess all project applications. with the blessing of the Panel, the Director may, in confidence, forward the Radiological Research Trust's recommendation to another grant-giving body We have been encouraged by other trusts in the belief that this will carry real weight

So, although we cannot yet finance you, please do consider the advantages of submitting projects to us at the same time as you submit them elsewhere We hope to have our Panel working by the end of February

The British Institute of Radiology and the Royal College of Radiologists have provided the financial support to create the Trust, but it is now an independent organisation and will have to make its own way in the world. It is to have a long future

Please tell people, both within and outside the profession, about the Trust Good radiological research can be very cost-effective in the betterment of diagnosis, care and treatment

The potential researchers are desperate for funds We can accept donations, covenants and bequests of all sizes, and shall be very sympathetic to named gifts or those dedicated for particular purposes.

For further information, please write to the Director, Professor E P G H. du Boulay, C B E., F R C R, F R C.P., 36 Portland Place, London W1N 3DG

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Press releases

Magnetic Resonance for Guy's Hospital, London

An agreement was signed on August 16, 1985, between Philips Medical Systems, London and the United Medical and Dental Schools of Guy's and St Thomas's Hospitals (University of London) for a Magnetic Resonance (MR) facility.

This major project covers the construction of an MR imaging suite on the Guy's Hospital site, the equipping of the building, the installation of a Philips Gyroscan MR imaging system, and the installation of a smaller MR spectroscopy unit in a special laboratory in the Guy's tower block

A joint research agreement between Philips and the United Medical Schools will initially cover two main areas. the use of a whole-body MR imaging system for *in-vivo* spectroscopy, and the use of MR for blood-flow imaging

The Gyroscan is capable of producing images in any plane from any part of the human body and will also be equipped to perform spectroscopic analysis. The two MR units will be able to exchange spectroscopic data It is hoped that this will allow direct correlation of data from live patients with data from specimens of known pathology, and thereby lead to a greater understanding of the way human tissues develop in a wide variety of diseases

For further information contact Philips Medical Systems Division, Building QM, 5600 MD Eindhoven, The Netherlands (Tel 040-762492)

The Marchig Animal Welfare Award 1986

The Marchig Animal Welfare Award, donated by Mme Jeanne Marchig of Geneva, serves the purpose of furthering the replacement of laboratory animals by alternative methods in scientific, commercial or educational fields. Appreciation will be expressed, thereby, to a person who makes an outstanding contribution to this specific scientific subject Contributions will be judged annually by a distinguished Panel and Resource Group. The value of the Award is Sw.Fr.40 000. The Award will be applicable to research work, teaching practice and the implementation of a new idea or technique, or of an existing but previously not implemented procedure, that will directly reduce the numbers of animals used

Further details of this Award and application forms for the competition are available from the Headquarters of the World Society for the Protection of Animals (WSPA), 106 Jermyn Street, London SW1Y 6EE, UK, and should be returned after completion to the Director-General of WSPA, with the contributions clearly marked "Marchig Animal Welfare Award", to arrive not later than September 30, 1986

The Awards Committee reserves the right not to make an award in any given year, if, in the opinion of the Committee, the projects submitted fail to meet the required standards of applied animal welfare

Library news

The BIR Library is open weekdays 9am–6pm

The Librarian, Mrs Gunnel Ingham, is in attendance Tuesdays and Thursdays 11am–4pm, Mrs Diana Jasper, daily 10am–6pm

The journal stock includes more than 100 titles Though journals may not be taken out of the library, there is a photocopy service, also available by post

Most books (excepting the historical collection) are available on loan.

Further information: telephone 01-580 4085

Recent additions to the Library

Brill, A B. (Ed) Low level radiation effects a fact book. 1982 with 1985 updates

Cancer treatment symposia, Vol 2 (1985) Proceedings of the Workshop on Radiotherapy for Lung Cancer

Cole, J D et al Graphical representation of K-shell and total internal conversion coefficients from z = 30–104. 1984

Hall, Eric J Radiation and life 2nd edit. 1984

Heimans, J. J., Valk, J & Lohman, A H. M. Angiographic anatomy of the anterior inferior cerebellar artery 1985

BIR Calendar Events

Unless otherwise indicated, enquiries about the following events should be addressed to the Assistant Secretary Programme, British Institute of Radiology, 36 Portland Place, London W1N 3DG (Tel. 01-580 4085)
The meetings are at 36 Portland Place unless otherwise stated
Attendance is open to non-members

Quantitation and New Techniques in Nuclear Medicine
February 12, 1986 at 10.30 am
Joint IPSM/BIR meeting

Lymphomas
February 20, 1986
The Finzi Lecture by Dr E. Glatstein. "Non-Hodgkin's Lymphomania"
Joint RSM/RCR/BIR all-day meeting organised by RSM.

Radiobiology Meeting
February 21, 1986 at 11.00 am
All-day general non-topic meeting organised by the Radiobiology Committee (proffered papers)

Clinical Use of Electrons
February 26, 1986 at 10 00 am
Chairmen: Dr W. F. White and Mr E G A Aird.
Speakers: Dr G Pitchford, Dr S. Klevenhagen, Dr M F. Spittle, Dr G. Ribeiro, Dr P. Williams, Mr K Larkin, Mr U Graf and Dr T. Landberg.
Joint BIR/IPSM meeting organised by BIR

Abdominal Sepsis
March 26, 1986
Including special lecture by Dr P C. Freeny
Joint RSM/RCR/BIR all-day meeting organised by RSM and held at the RSM.

Radiology '86
April 9–11, 1986
Bristol
44th Annual Congress and Exhibition
Incorporating the joint spring meeting of the Institute with the Royal College of Radiologists and the Section of Radiology of the Royal Society of Medicine It will be held in the picturesque setting of the Bristol waterfront.
The scientific programme (CME accredited) will encourage discussion of contemporary aspects of the radiological sciences and will include·
BIR Mackenzie Davidson Memorial Lecture (Dr A. Margulis "The Impact of New Imaging Technology on Health Care, Research and Teaching")
BIR Mayneord Lecture, sponsored by 3M UK Plc (Mr G Higson. "Seeing Things More Clearly")
RCR George Simon Lecture (Professor N. M. Bleehen. "Raleigh's Revenge")
All-day Seminar—Buying for Radiology organised with the Association of National Health Service Supplies Officers
All-day Seminar—Biological Basis of Radiological Protection and its Application to Risk Assessment
Proffered Papers
Large Technical and Scientific Exhibition
Annual Dinner, April 10

Annual Dinner
April 10, 1986
Holiday Inn, Bristol

Annual General Meeting of the BIR
May 14, 1986
Members only

Safety of Ultrasound and Presidential address
May 15, 1986
Middlesex Hospital Medical School, London W1
Includes the Presidential Address to be given by Dr P. N T. Wells: "The prudent use of ultrasound"

Progress in Tumour Radiobiology
May 16, 1986 at 11.00 am
Organised by the Radiobiology Committee (proffered papers).

The Assurance of Quality in Medical Imaging
May 21, 1986
Middlesex Hospital Medical School
All-day meeting organised by the Industry Committee.

Conversazione
June 19, 1986 at 7 00 pm
Royal Society of Medicine, London W1
Incorporating the Silvanus Thompson Memorial Lecture. "Seeing through illusion", by Professor R. L. Gregory

Joint RCR/BIR/RSM Autumn Provincial Meeting and RCR Annual General Meeting
September 11–13, 1986
University of Sheffield
Organised by the RCR

Meetings, Courses, Notices

As a service to our readers, the title, date and place of meetings and contact address will be inserted free of charge: any additional information will be charged at £1.50 per printed line, per insertion. Please contact the Managing Editor.

Clinical Oncology Symposium: Investigation Techniques in Radiation Oncology
February 21–22, 1986
Jarvis Hall, 66 Portland Place, London
Further details The Meetings Secretary, The Royal College of Radiologists, 38 Portland Place, London W1N 3DG (Tel. 01-636 4432/3).

Symposium on Dysphagia
February 27–March 1, 1986
The Johns Hopkins Medical Institutions, Baltimore, Maryland
Further details. Jeanne Ryan, Program Coordinator, Office of Continuing Education, The Johns Hopkins University School of Medicine, 720 Rutland Avenue, Turner 22, Baltimore, MD 21205, USA (Tel 301-955 6046).

International Continuing Medical Education Series
Controversies in Medicine
February 28–March 28, 1986
Barbados

April 30–May 15, 1986
Paris/Versailles, France

August 14–29, 1986
London, England

Update on Laser Therapy
June 25–July 10, 1986
Heidelberg, Germany

Further details Dr Barry M Manuel, Department of CME, Boston University School of Medicine, 80 E. Concord Street, Boston, MA 02118, USA (Tel. 617-638 4605).

Interventional Radiology Course
March 3–7, 1986
Hotel St George, Sheffield
Further details: Dr D. C. Cumberland, Northern General Hospital, Sheffield S5 7AU (Tel 0742-387253 ext.4828).

Computers in Medicine—A Workshop for Beginners
March 10–11, 1986
Monte Carlo
Further details: Computers in Medicine, Dr Hans O. Beckmann, Bitterstr 13, D 1000 Berlin 33, West Germany.

International Symposium on the Optimization of Radiation Protection
March 10–14, 1986
Organised by the International Atomic Energy Agency, Vienna, Austria.
Closing date for applications to attend (via Department of Energy) December 13, 1985.
Further details. Mr M. Pankhurst, Atomic Energy Division, Department of Energy, Thames House South, Millbank, London SW1P 4QJ

European Workshop on Nuclear Magnetic Resonance in Medicine—4th Annual Meeting Joint Meeting with World Health Organization
March 12–15, 1986
Monte Carlo
Further details. European Workshop on NMR in Medicine, Dr R. N Muller/Dr P A Rinck, State University of Mons, Medical Faculty, B 7000 Mons, Belgium (Tel 32-65-315171 ext 228)

3rd Congress of the South African Medical Ultrasound Society
March 14–17, 1986
Johannesburg Sun
Further details: Congress Director, PO Box 6705, Johannesburg 2000, South Africa

Combined Course in Clinical Oncology and Radiotherapeutics
March 17–21, 1986
The Postgraduate Medical Centre, Lancaster House, Glasgow
Further details and application forms: Dean of Postgraduate Medicine, University of Glasgow, Glasgow, G12 8QQ (Tel 041-339 8855, ext 7274).

Obstetric and Neonatal Blood Flow
April 8–9, 1986
King's College Hospital, London
Further details. Biological Engineering Society, Royal College of surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN (Tel. 01-242 7750)

The Actinides
April 9, 1986
City Conference Centre, 76 Mark Lane, London EC3
This meeting is organised by the Society for Radiological Protection and will be followed by the Society's Annual General Meeting
Further details. Programme Committee Secretary, Professor J H. Martin, Department of Medical Biophysics, Building 15, Park Wynd, University of Dundee, Dundee DD1 4HN.

Symposium on Malignant Disease and the Skin
Departments of Dermatology and Radiation Oncology
April 11–12, 1986
Subjects include epidemiology, pathogenesis and therapy.
Speakers include Prof J A. A. Hunter, Edinburgh, Dr John White, Southampton, Dr Neil Smith, London, Prof Wilson-Jones, London, Dr A Chu, London, Dr S. S Bleehen, Sheffield, Dr Margaret Spittle, London. Accommodation.University Hall of Residence
Registration fee £25 00
Further details Prof C F. H. Vickers, Department of Dermatology, Royal Liverpool Hospital, or Dr M J Garrett, Department of Radiation Oncology, Clatterbridge Hospital, Bebington, Wirral

British Nuclear Medicine Society Annual Congress
April 13–16, 1986
at Imperial College, London SW7
Further details Mrs A Taylor, BNMS, Conference Secretary, 22 Leinster Avenue, East Sheen, London S14 7JP

Biological and Therapeutic Aspects of Cancer Metastasis
April 14–17, 1986
Vitoria, Spain
The University of the Basque Country (Northern Spain) is organising an International Conference on the "Biological and Therapeutic Aspects of Cancer Metastasis" Topics include immunological and therapeutic aspects in cancer metastasis, host factors in metastasis, organ specificity, genetic heterogeneity of tumour cells, phenotypic heterogeneity of tumour cells, cell membranes and tumour cell-connective tissue interactions. Guest speakers include: E. Barberá, R. Feldman, I Fidler, R. Kefford, R. Kerbel, L. Olsson, G Poste, M. F. Poupon, V Schirrmacher and D Tarin.
Further details. Conference Secretariat, Apartado 1299, 48080 Bilbao, Spain.

Images of Living Brain Chemistry: Neuroreceptors
April 18–19, 1986
Baltimore, Maryland
Further details. Diane Heydinger, Program Coordinator, Turner 22, 720 Rutland Avenue, Baltimore, MD 21205, USA (Tel. 301-955 6046).

The National Institutes of Health Consensus Development Conference on Neurological Applications of Positron Emission Tomography
April 21–23, 1986
Clinical Center of the National Institutes of Health, Bethesda, Maryland
Further details Shelley Clark (Tel 301-468 6555).

Course on Cancer Epidemiology
April 28–May 9, 1986
Holzhau, East Germany
Further details The Research Training and Liaison Unit, International Agency for Research on Cancer, 150, cours Albert Thomas, 69372 Lyon Cedex 08, France

1st International Conference on the Clinical Application of Photosensitization for Diagnosis and Treatment
April 30–May 2, 1986
Tokyo
Topics will include tumour localisation and treatment in cancer of various organs, including combined treatment with other modalities
Further details. Dr Yoshihiro Hayata, Tokyo Medical College Hospital, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan

Radiology of the Small Intestine
May 31, 1986
John Radcliffe Hospital, Oxford
Fee. £30 00
Particular emphasis will be placed on the small bowel enema technique.
Further details Dr D. J Nolan, Department of Radiology, John Radcliffe Hospital, Oxford OX3 9DU (Tel. 0865-817238)

IV Symposium on the Medical Applications of Cyclotrons
May 28–31, 1986
Turku, Finland
Further details: Scientific Secretary, Robert Paul, Turku Medical Cyclotron Project, University Hospital, SF-20520, Turku, Finland (Tel: (21) 611 611).

European Gamma-11 Users Meeting
June 4–6, 1986
Guy's Hospital, London
Further details. E. D Williams, Medical Physics Department, Sunderland District General Hospital, Sunderland SR4 7TP
Further details Dr Yoshihiro Hayata, Tokyo Medical College Hospital, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan

Cambridge Meeting on Chest Disease
July 3–5, 1986
King's College, Cambridge
This residential meeting should be of interest to Consultants and experienced Senior Registrars. The format will be as in previous years and the numbers will be limited
Further details. Dr C D R Flower, Department of Radiology, Addenbrooke's Hospital, Hills Road, Cambridge

The Leeds Gastroenterology Course for Radiologists
July 7–11, 1986
St James's University Hospital, Leeds
Further details Mr Frank Moran, Senior Administrative Assistant, Postgraduate Dean's Office, Leeds General Infirmary, Leeds LS1 3EX (Tel 0532-432 799, ext. 3631)

Nato Advanced Study Institute on: Physics and Technology of Hyperthermia
July 26–August 9, 1986
Urbino, Italy
Further details Dr S. B. Field, MRC Cyclotron Unit, Hammersmith Hospital, Ducane Road, London W12 0HS

Computers for the Practising Physician: Update 1986
July 27–30, 1986, New Seabury, Cape Cod, Massachusetts
Further Details: Department of CME, Boston University School of Medicine, 80 East Concord Street, Boston, MA 02118, USA.

4th International Congress on Interventional Ultrasound.
August 19–22, 1986
Copenhagen, Denmark
Further details: Spadille Congress Service, DK-3100 Hornbaek, Denmark

International Symposium on Radiotherapy in Developing Countries: present status and future trends
September 1–5, 1986
Vienna
To be convened by the International Atomic Energy Agency. Papers to be submitted by February 14, 1986
Further details M. Pankhurst, Atomic Energy Division, Department of Energy, Thames House South, Millbank, London SW1P 4QJ (Tel 01-211 6850).

4th Midlands Course in Otoradiology
September 12–13, 1986
Coventry
Further details. Miss M Adams, Centre Administrator, Warwickshire Postgraduate Medical Centre, Stoney Stanton Road, Coventry CV1 4FG

4th International Selectron Users Meeting
September 14–17, 1986
British Columbia, Canada
Further details Dr S M. Jackson, Cancer Control Agency of BC, 600 West 10th Avenue, Vancouver, BC, Canada V5Z 4E6

Blood Flow in the Brain
September 23–25, 1986
Strathclyde University, Glasgow
Further details Biological Engineering Society, Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN (Tel. 01-242 7750).

Conference on the Interaction of Radiation Therapy and Chemotherapy
September 28–October 1, 1986
The Fort Magruder Inn, Williamsburg, Virginia
Further details. Ms Suzanne Bohn, American College of Radiology, 925 Chestnut Street, Philadelphia, PA 19107 USA (Tel. 215-574 3181)

International Conference on Prostaglandin and Lipid Metabolism in Radiation Injury
October 1–3, 1986
Washington D C
Further details Dr Thomas L Walden, Biochemistry Department, Armed Forces Radiobiology Research Institute, Bethesda, Maryland 20814-5145 USA.

AER Symposium 1986 Tumours and Imaging
October 1–4, 1986
Vienna Hilton Hotel, Austria
Congress President Prof H. Pokieser, c/o Wiener Medizinische Akademie, Alser Strasse 4, A-1090 Wien, Austria (Tel 222-421 383)

Age-Related Factors in Radionuclide Metabolism and Dosimetry
November 26–28, 1986
Angers
Further details. Dr G. B. Gerber, Commission of the European Communities, DG XII/FI, Rue de la Loi 200, B-1049 Brussels, Belgium (Tel. 02-235 4041)

Asian Regional Conference of The International Organisation for Medical Physics
December 8–12, 1986
Bombay, India
Further details: Organising Secretary. Asian Regional Conference on Medical Physics 1986, Association of Medical Physicists of India Division of Radiological Protection, Bhaba Atomic Research Centre, Bombay 400 085, India.

VI Congress of the European Association of Radiology (ECR '87)
May 31–June 6, 1987
Lisbon, Portugal
Further details: Secretariat ECR '87, SPRMN, Av. Elias Garcia, 123–7° DTo, 1000 Lisboa, Portugal, (Tel. 77-05 30), Telex 62074 SPRMN P

Ninth International Conference on the Use of Computers in Radiation Therapy
June 22–25, 1987
The Hague
Further details: Organisation IX ICCR, Ir P H. van der Giessen, Dr. Bernard Verbeeten Institute, P.O Box 90120, 5000 LA Tilburg, The Netherlands, (Tel 013 655 725).

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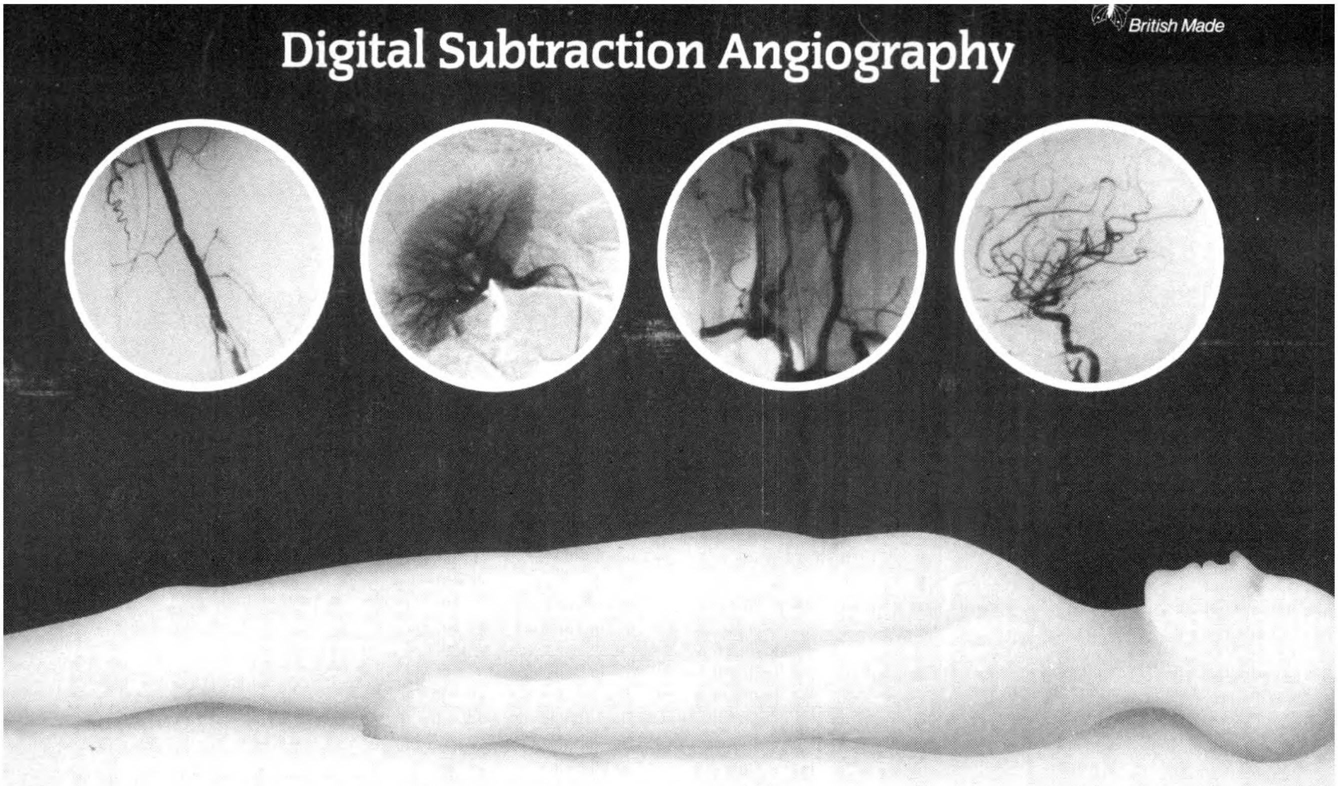
The third Mayneord Lecture entitled **Seeing things more clearly** will be given by Mr G. R. Higson BSc, FInstP, CEng, FIEE, Director, Scientific and Technical Services, Department of Health and Social Security. It will be given at the Unicorn Hotel, Bristol, on Wednesday 9th April 1986 at 5.00 pm during the BIR Annual Congress RADIOLOGY '86.



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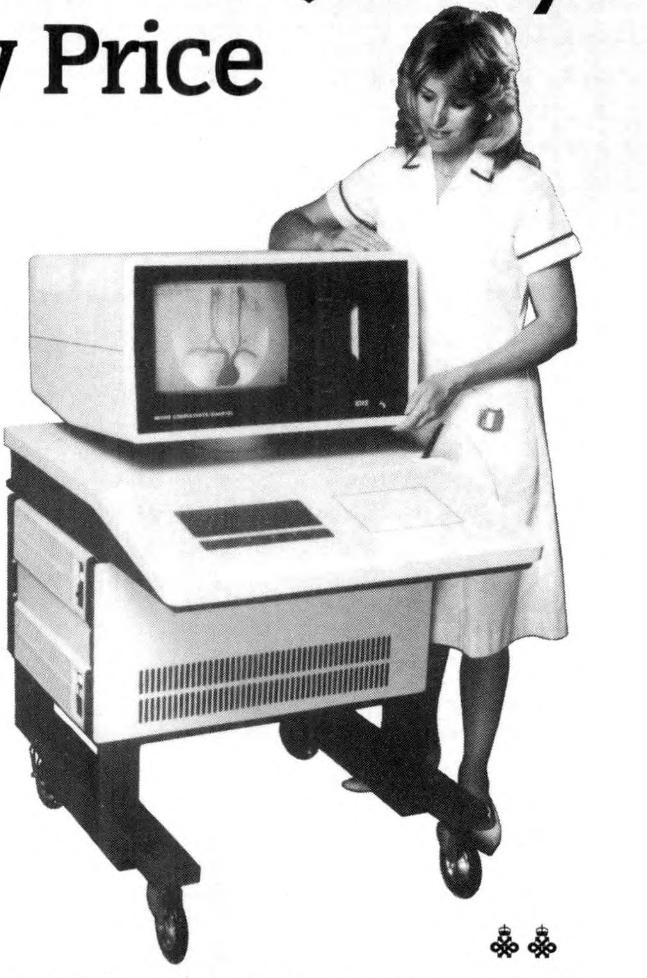

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Correspondence
Agreement of quadratic and CRE models in predicting the late effects of continuous low dose-rate radiotherapy 193
J. A. O'Donoghue
Reply
R. G. Dale
A randomised comparison of photons and 15 MeV neutrons for the treatment of carcinoma of the bladder 195
M. Catterall and D. K. Bewley
Instability of radiation protection quantities 195
J. R. Greening
Spread of testicular tumour to the contralateral groin: another case 196
P. von Rottkay
Corrections 106 156

Book reviews

Diagnostic ultrasound of the lower abdomen. *A. Trenta, P. Pavlica, G. Stasi, R. Tonti and G. Viglietta* 96
Ultrasound annual 1984. *R. C. Sanders and M. C. Hill* (Eds) 96
Angiographic diagnosis of supratentorial cerebral tumours (compared with CT scan). *A. Pansini and P. Conti* 106
Nuclear magnetic resonance (NMR) imaging. *C. L. Partain, A. E. James Jr, F. D. Rollo and R. R. Price* 126
Nuclear magnetic resonance imaging—basic principles. *S. W. Young* 126
Clinical magnetic resonance imaging. *A. R. Margulis, C. B. Higgins, L. Kaufman and L. E. Crooks* (Eds) 126
Diagnostic imaging in hemophilia. *H. Pettersson and M. S. Gilbert* 130
1985 year book of nuclear medicine. *P. B. Hoffer* (Ed.) 152
Diagnostic imaging in clinical medicine, 3rd edit. *R. H. Troupin* 152
Nuclear medicine annual 1985. *L. M. Freeman and H. S. Weissmann* (Eds) 152
The principles and practice of ultrasonography in obstetrics and gynaecology, 3rd edit. *R. C. Sanders and A. E. James* (Eds) 163
Computed tomography of the head and neck. Contemporary issues in computed tomography, Vol. 5. *B. L. Carter* (Ed.) 164
Computed tomography of the pelvis. Contemporary issues in computed tomography, Vol. 6. *J. W. Walsh* (Ed.) 164
Imaging in pediatric oncology. *J. H. Miller* (Ed.) 170
Ultrasound of the infant brain. *M. I. Levene, J. L. Williams and C.-L. Fawer* 170
Pediatric nuclear medicine. *S. T. Treves* 170
Medical effects of ionizing radiation. *F. A. Mettler and R. D. Moseley* 186
Radiation Protection in Hospitals. *R. F. Mould* 192
Book received 196
BIR Bulletin and Calendar Events *facing page* 196

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★ All day Seminar—Biological Basis of Radiological Protection and its Application to Risk Assessment
★ Proffered Papers (late submissions will be considered)
★ Large Technical and Scientific Exhibition

For further information and registration details please apply to:

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The British Institute of Radiology 36 Portland Place London W1N 3DG (Telephone 01 580 4085)

VOL 59 NO 698 FEBRUARY 1986

The British Journal of Radiology

Contents

Page

Editorial 95

The combination of radiotherapy and surgery in the treatment of carcinoma of the uterine cervix 97
G. Wiernik

A clinical phase I toxicity study of Ro 03-8799: plasma, urine, tumour and normal brain pharmacokinetics 107
J. T. Roberts, N. M. Bleehen, M. I. Walton and P. Workman

Antibody-guided radiolocalisation of tumours in patients with testicular or ovarian cancer using two radioiodinated monoclonal antibodies to placental alkaline phosphatase 117
A. A. Epenetos, D. Carr, P. M. Johnson, W. F. Bodmer and J. P. Lavender

Comparison of radiosensitivities of human autologous normal and neoplastic thyroid epithelial cells 127
R. C. Miller, K. J. Kopecky, T. Hiraoka, H. Ezaki and K. H. Clifton

Accuracy of radiological staging procedures in non-seminomatous testis cancer compared with findings from surgical exploration and histopathological studies of extirpated tissue 131
L. Samuelsson, L. Forsberg and A. M. Olsson

Angiography in transient cerebral ischaemia using three views of the carotid bifurcation 135
W. D. Jeans, S. Mackenzie and R. N. Baird

Contrast media in double-contrast arthrography of the knee: a comparison of ioxaglate and iothalamate preparations 143
C. Ingram and D. J. Stoker

Radioaerosol assessment of mucociliary clearance: towards definition of a normal range 147
J. E. Agnew, P. P. Sutton, D. Pavia and S. W. Clarke

Assessment of priorities when introducing some radiation protection methods in radiodiagnosis 153
J. G. B. Russell

The use of carbon fibre material in table tops, cassette fronts and grid covers: magnitude of possible dose reduction 157
A. P. Hufton and J. G. B. Russell

The risk of diagnostic radiation of the newborn 165
E. W. L. Fletcher, J. D. Baum and G. Draper

Case reports

Complete regression of pulmonary metastases from malignant melanoma of the vulva following therapy with tamoxifen 171
R. Amin

Erdheim–Chester disease presenting as malignant exophthalmos 173
I. Rozenberg, J. Wechsler, F. Koenig, B. Brun, D. Larde, Y. Raulo, J. Hazard, Y. Pinaudeau and G. Coscas

Altered anterior axillary fold in radical mastectomy still present after breast reconstruction 178
G. Rubin

Disc calcification in childhood: computed tomographic and magnetic resonance imaging appearances 180
J. C. McGregor and P. Butler

Cutaneous seeding of pancreatic carcinoma by fine-needle aspiration biopsy 182
H. J. C. Rashleigh-Belcher, R. C. G. Russell and W. R. Lees

Ultrasonography of hepatic portal venous gas due to diverticulitis 183
S. Fataar, E. Cadogan and O. Spruyt

Case of the month

The case of the bulging Bulgarian 187
Z. Halpern, M. Averbuch, J. Papo, R. Shilo and Y. Levo

Short communications

Artefactual results with CHIP perhydrate 189
E. Smith and A. H. W. Nias

A preliminary study of the possible benefits of using carbon dioxide insufflation during double-contrast barium enema 190
D. S. Grant, C. I. Bartram and C. W. Heron

(continued on inside back cover)

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Volume 59 Number 699
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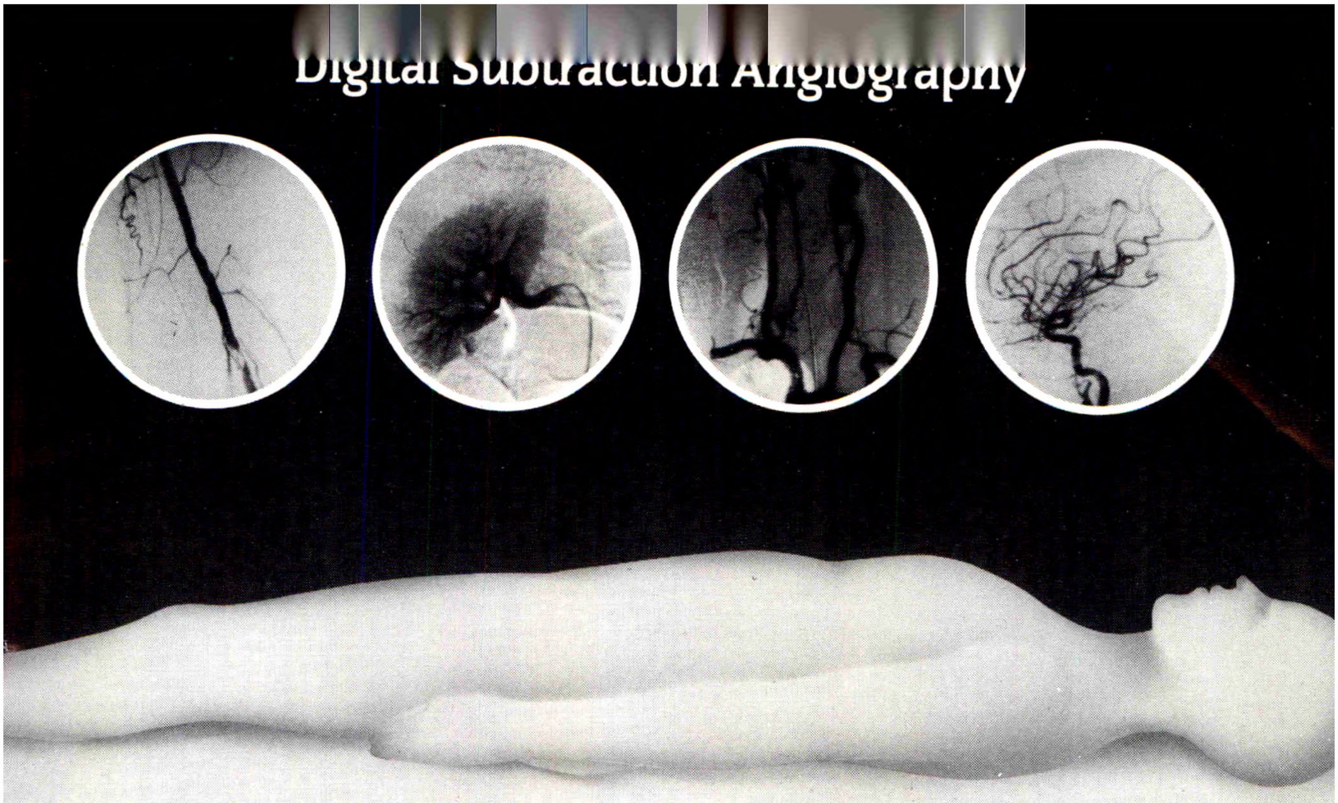

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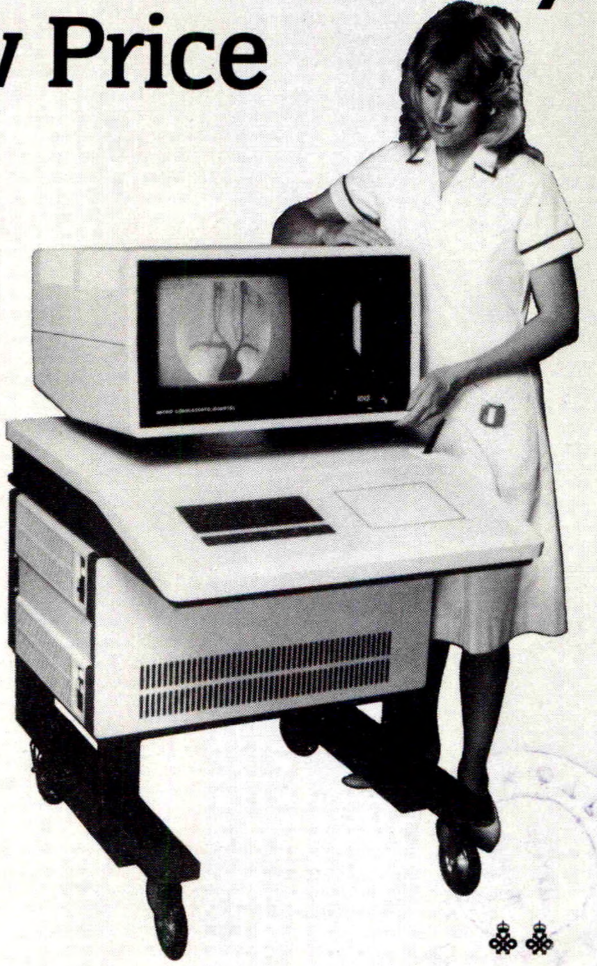

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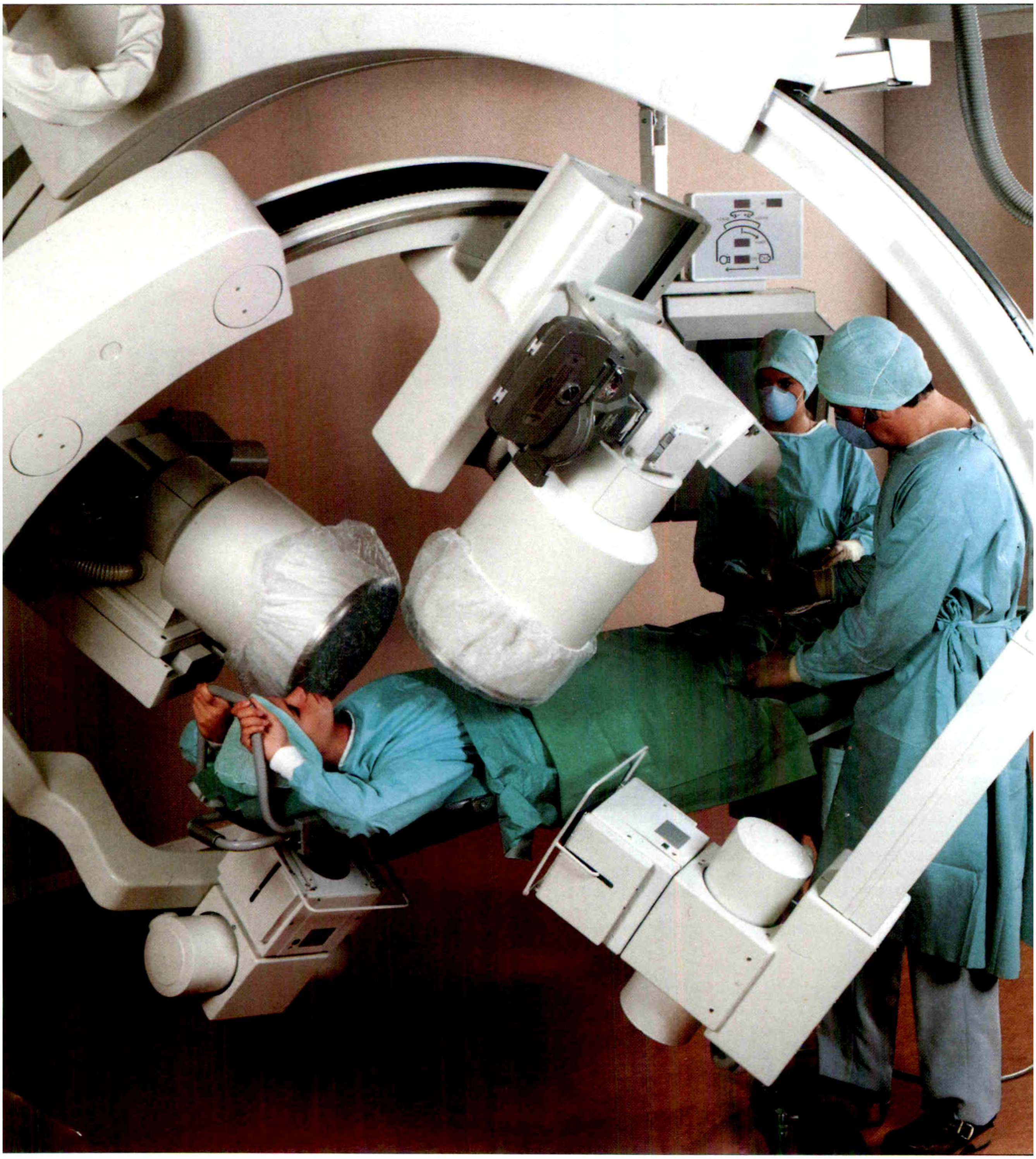

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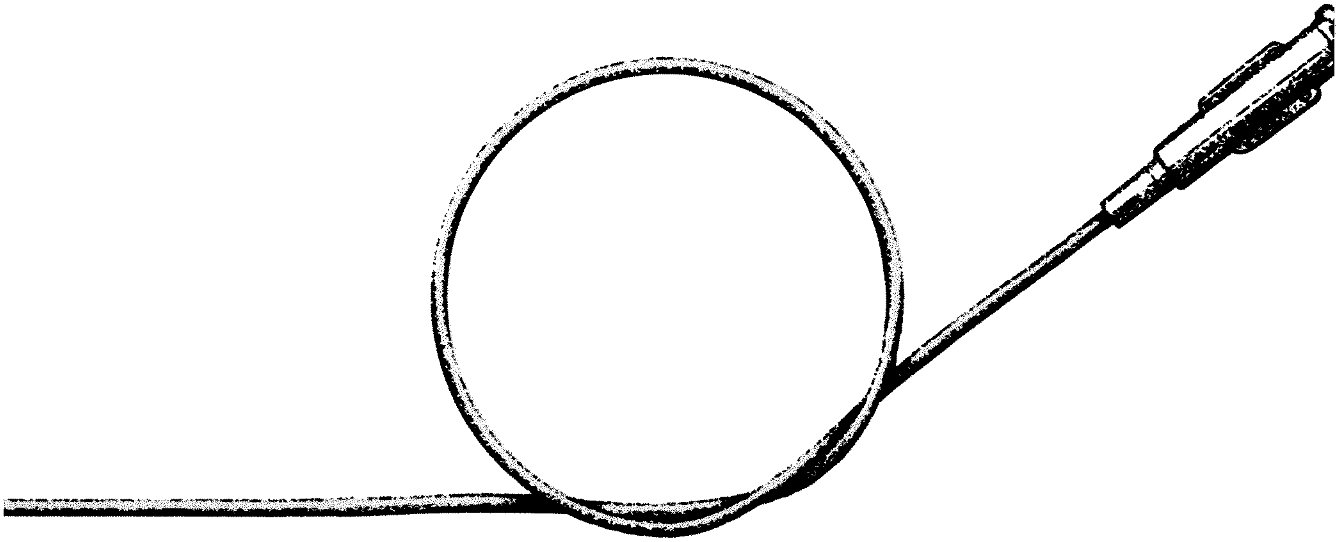

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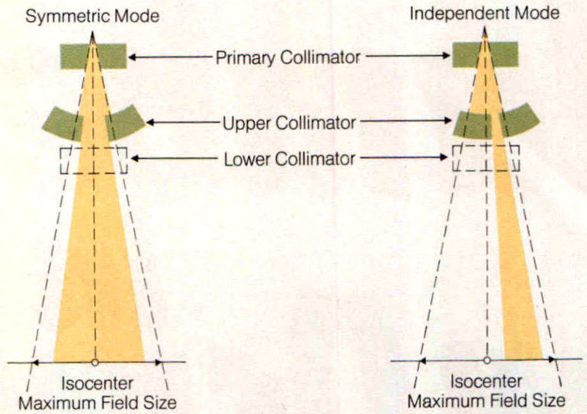

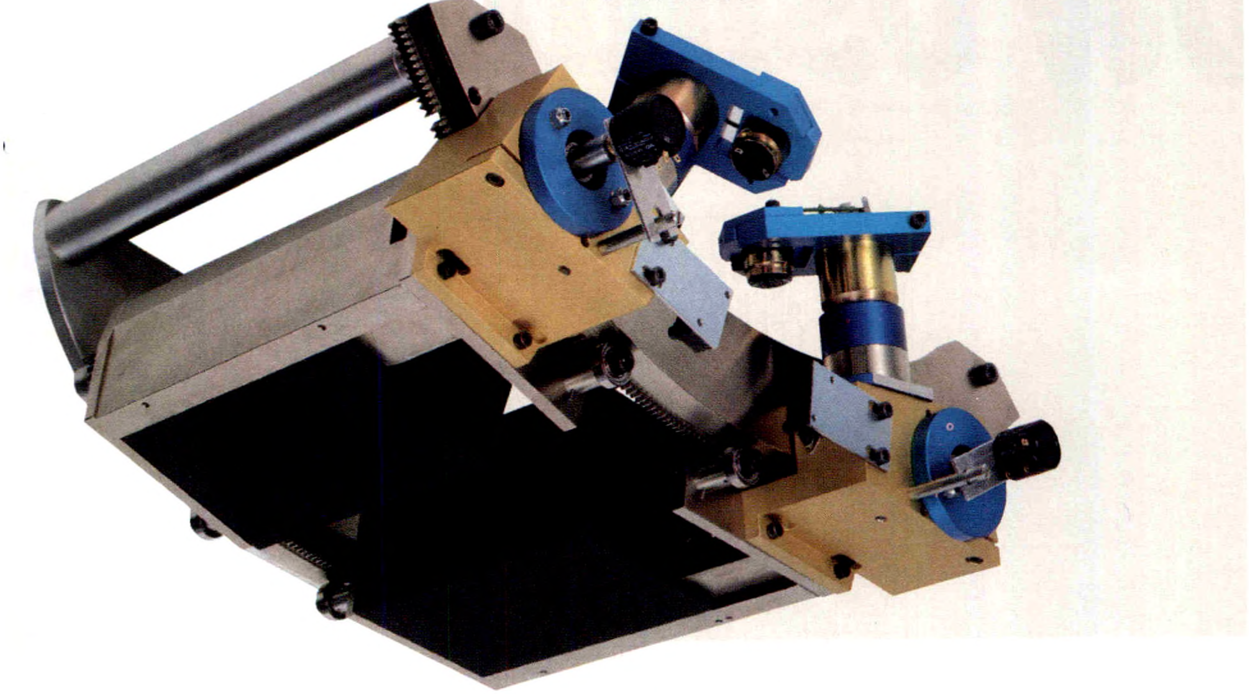

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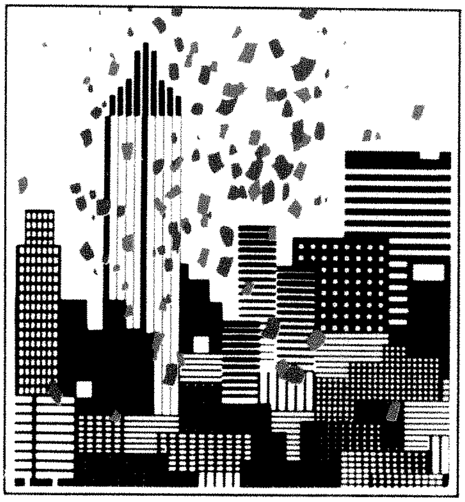

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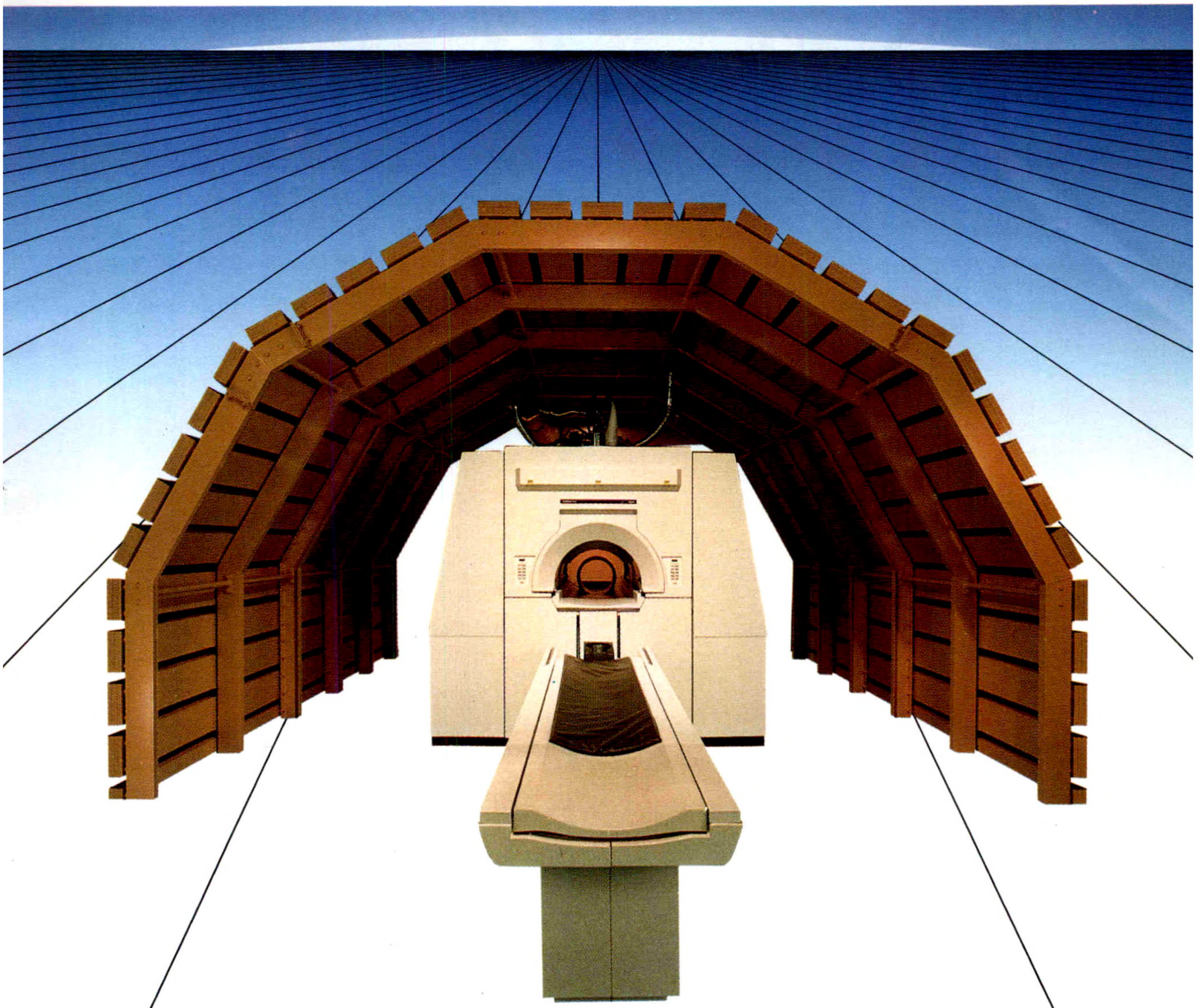

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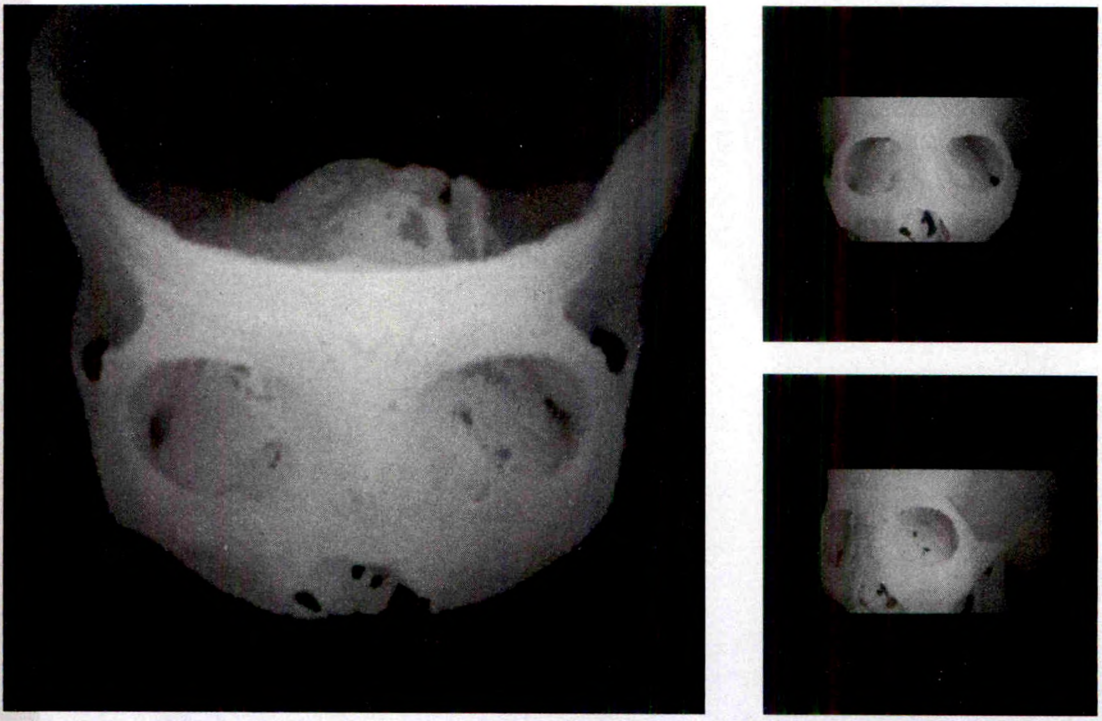

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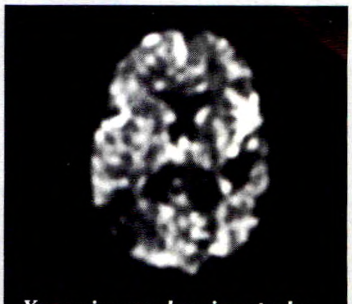
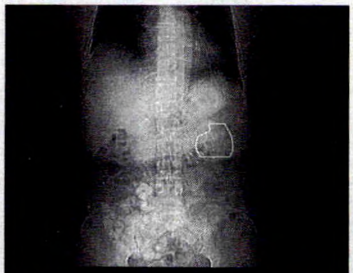
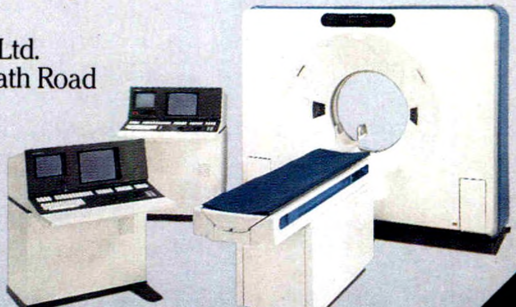


Xenon image showing stroke one day after left MCA incident



Correlate plot for surgical and radiation planning.



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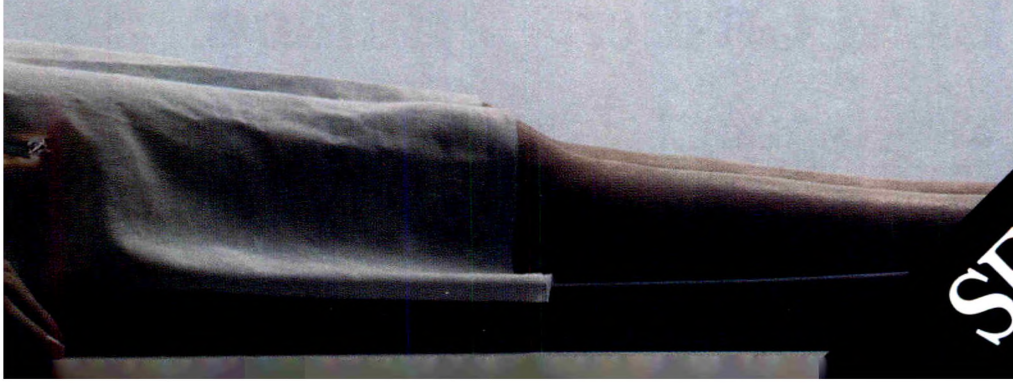

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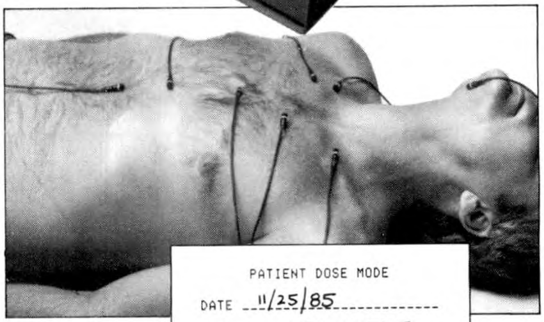

```
            PATIENT DOSE MODE
DATE __11/25/85______________
TREATMENT _AP MANTLE_________
USING DETECTOR SET A
PATIENT
_________MARY DOE____________
BY ______JACK SMITH__________

DETECTOR     LOCATION       DOSE
--------     --------       ----
1(ALM)RED  _CHIN__________    15
2 ORANGE   _LT NECK_______   215
3 YELLOW   _RT NECK_______   216
4 LT GRN   _LT SUPRACLAV__   208
5 DK GRN   _RT SUPRACLAV__   213
6 LT BLUE  _LT AXILLA_____   215
7 DK BLUE  _RT AXILLA_____   215
8 BLK      _CENT AXIS_____   203

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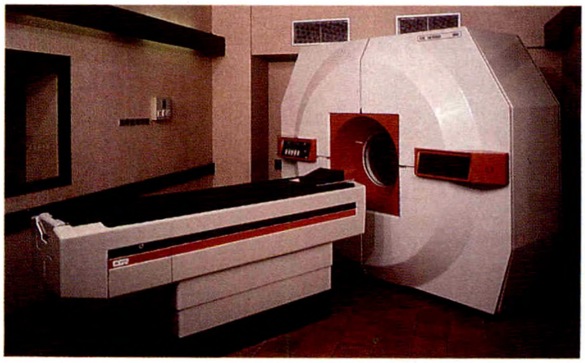

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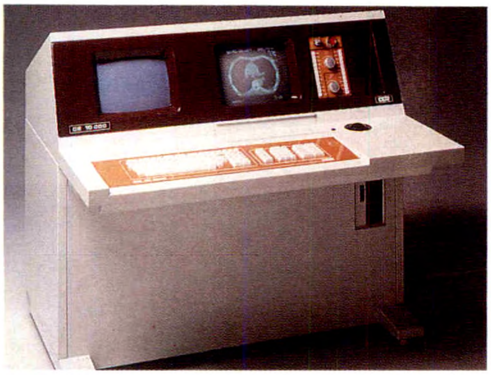

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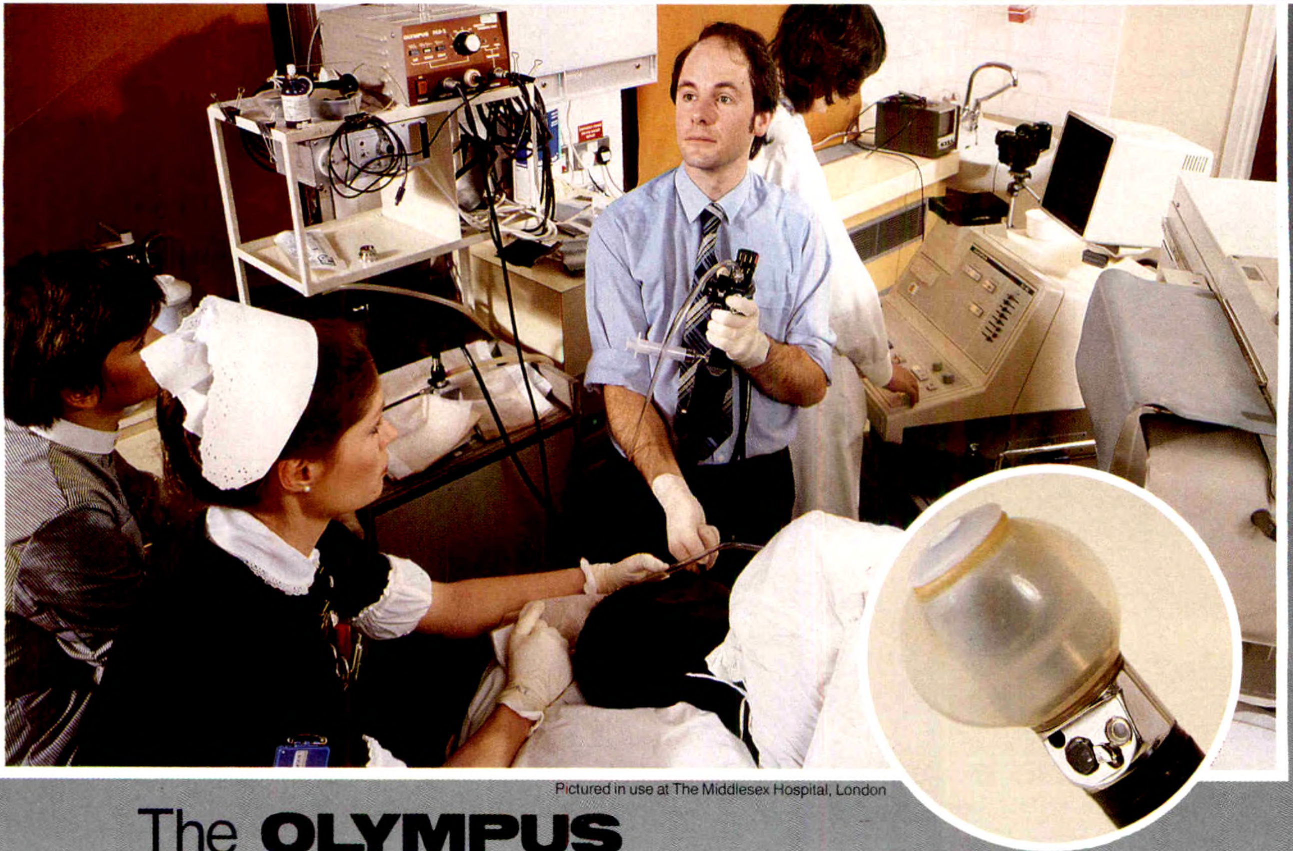

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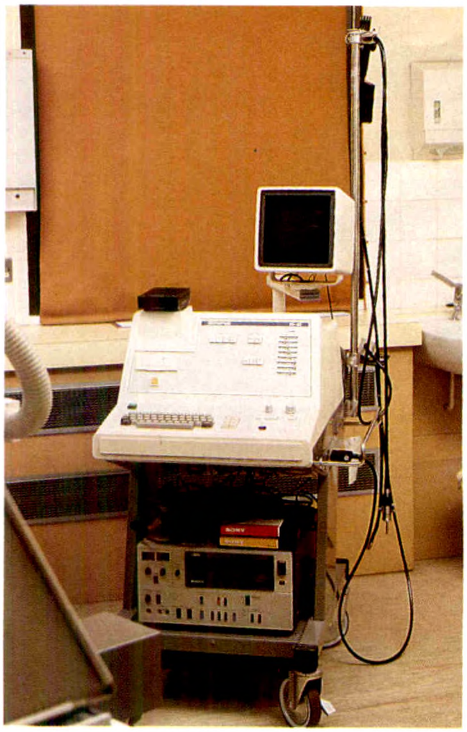

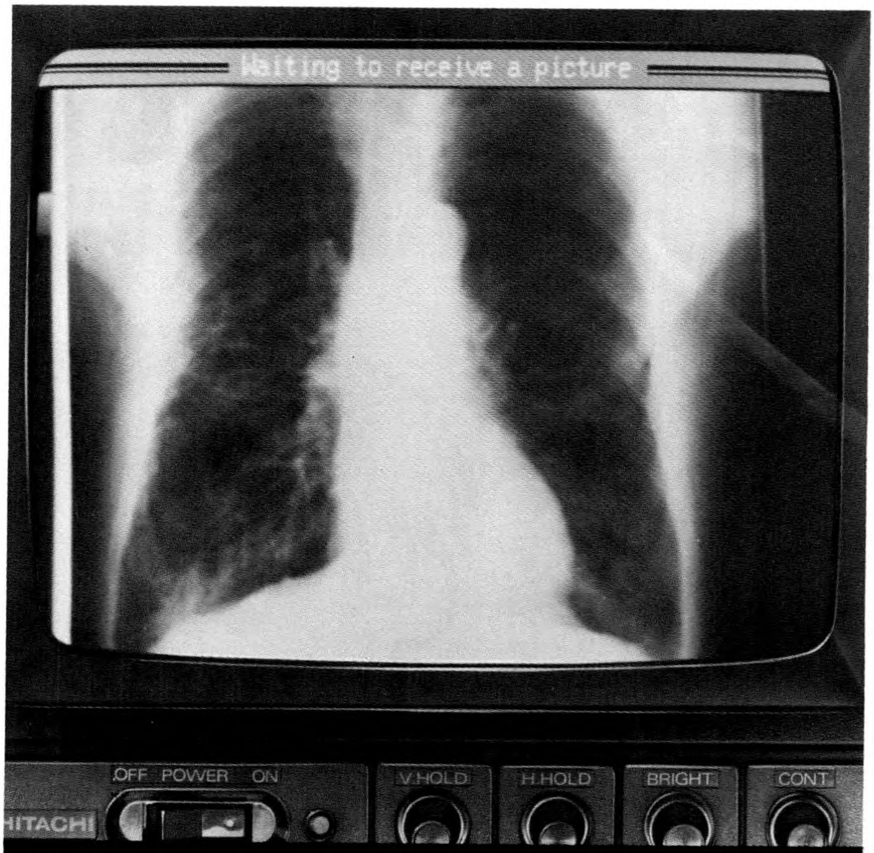

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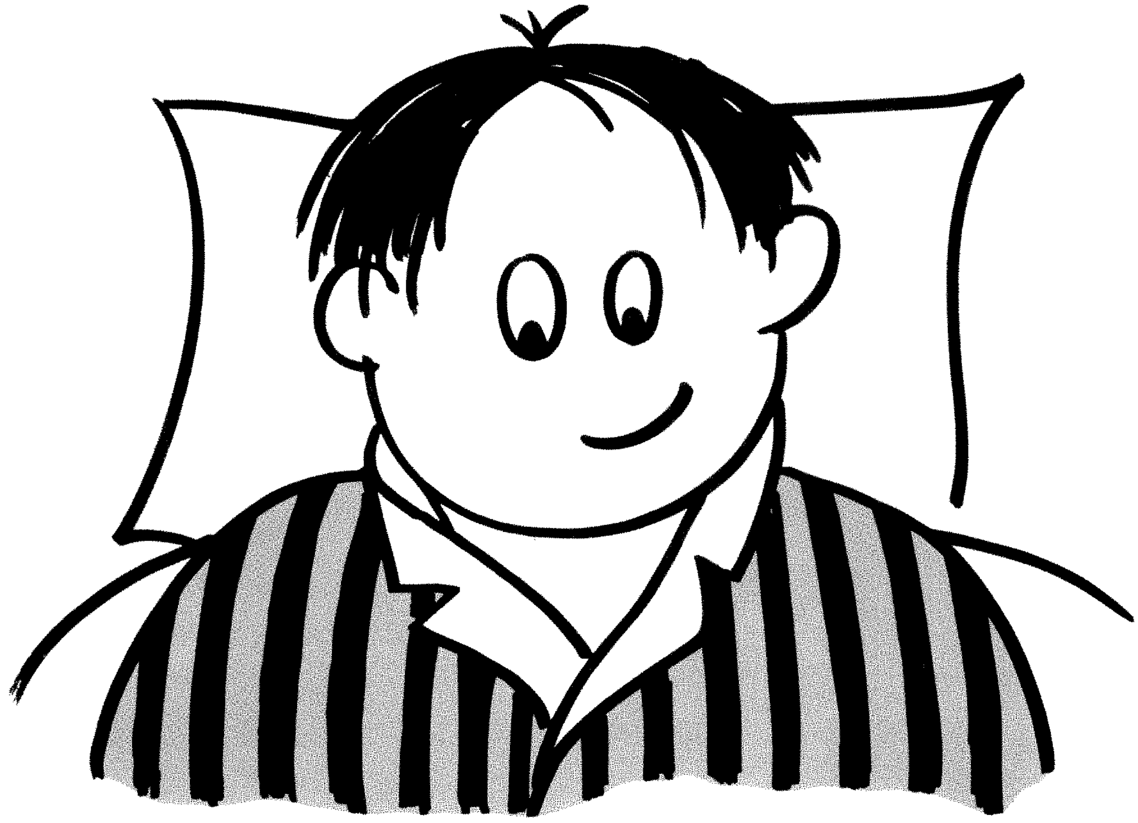

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The British Journal of Radiology

Cartilage-cell-containing tumours of the pelvis: a radiological review of 40 patients

By Graham Buirski, M.R.C.P., F.R.C.R., *A. H. C. Ratliff, Ch.M., F.R.C.S. and *Iain Watt, M.R.C.P., F.R.C.R.

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ABSTRACT

Cartilage-cell-containing tumours of the pelvis are responsible for a quarter of all primary bone lesions in this site. Benign tumours are uncommon but when present have classical radiological appearances similar to those described elsewhere. Only the rarest, chondromyxoid fibroma, may cause difficulty in diagnosis. Seventy-three per cent of cartilage-cell tumours are malignant and are either chondrosarcoma or chondroblastic osteosarcoma. Chondrosarcoma occurs after the second decade of life, usually with a longer history, and may be categorised as either a secondary peripheral or primary central tumour, each having typical radiological features. Chrondroblastic osteosarcoma tends to occur in younger patients with a shorter clinical history and is almost exclusively situated adjacent to a sacroiliac joint, producing purely lytic, sclerotic or mixed patterns of bone destruction. Experience suggests that computed tomography is the single most valuable further examination, since the pelvis is a complex structure with confusing overlying soft-tissue artefacts. This technique may indicate both the route and choice of optimal biopsy site.

Primary bone tumours are rare, often causing diagnostic difficulty. Those arising in the bony pelvis may be particularly confusing since their radiological characteristics are sometimes at variance with those of similar tumours arising in more familiar sites in the appendicular skeleton. This may be due, in part, to the flat bone origin of the ilia, or because the pelvis is difficult to image, since overlying bowel gas may obscure small lesions. Similarly, tumours of the pelvis may be difficult to assess and manage clinically because symptoms may be poorly localised and lesions may be quite large before they present.

This paper reviews primary tumours arising in the pelvis which contain cartilage cells. These may be particularly difficult to distinguish histologically and radiology plays an important role in the primary diagnosis. They have been reviewed in order to delineate any differences between them and their kindred arising elsewhere in the appendicular skeleton and in order to establish whether or not distribution patterns may assist diagnosis.

METHODS

All primary cartilage-containing tumours of the pelvis classified by the Bristol Bone Tumour Registry have been reviewed. The Registry records extend from 1946. Early cases had plain radiographs and tomograms available for review, whereas more recent patients also had further investigations, including arteriography, scintigraphy and computed tomography (CT). Attention was paid particularly to plain radiographic and tomographic appearances, since these were the images at presentation upon which clinical and management decisions had been, and still are, frequently based. The distribution and individual clinical and radiological characteristics of these tumours were reviewed and documented.

RESULTS

Tumours containing cartilage cells were identified in 40 of 151 cases (26%) of all primary pelvic bone tumours documented by the Bristol Bone Tumour Registry. The histological types are listed in Table I, the majority (73%) were malignant.

Benign tumours

Whilst the age at presentation varied, all but two of the 11 patients were older than 21 years (Fig. 1). The sexes were equally involved. Eight patients complained of increasing pain in the hip, buttock or thigh; two of these also had a palpable mass. Two patients were

TABLE I

PRIMARY CARTILAGE TUMOURS OF THE PELVIS: INCIDENCE OF HISTOLOGICAL TYPES

	No. of patients
Benign	
Osteochondroma	6
Chondroma	2
Chondroblastoma	2
Chondromyxoid fibroma	1
Total	11
Malignant	
Chondrosarcoma	20
Chondroblastic osteosarcoma	9
Total	29
Total	40

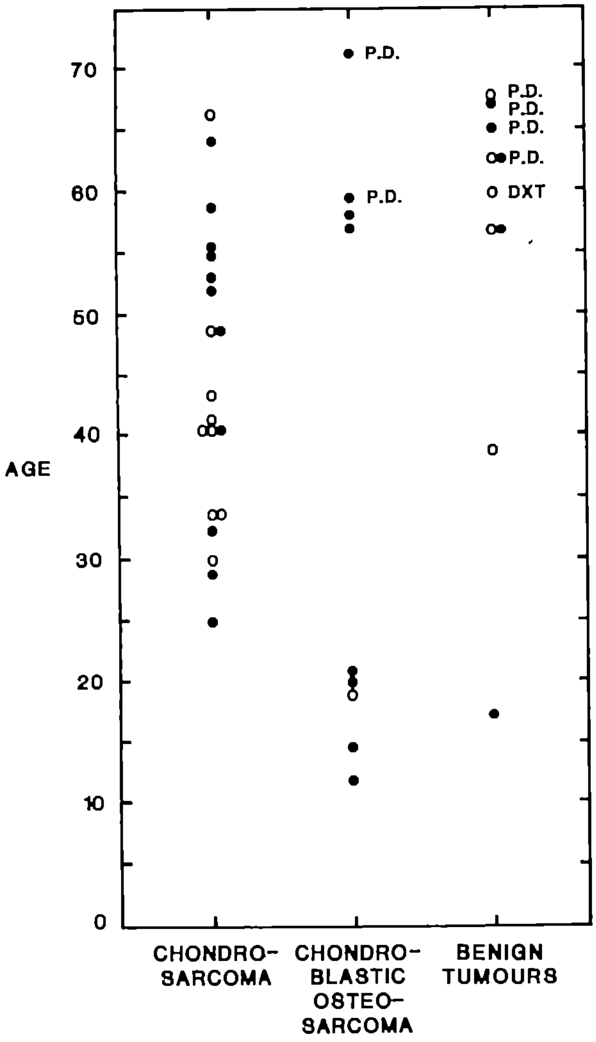

FIG 1.

Age distribution of 37 patients with benign tumours, COS and CS (P.D = Paget's disease, DXT = post-irradiation).

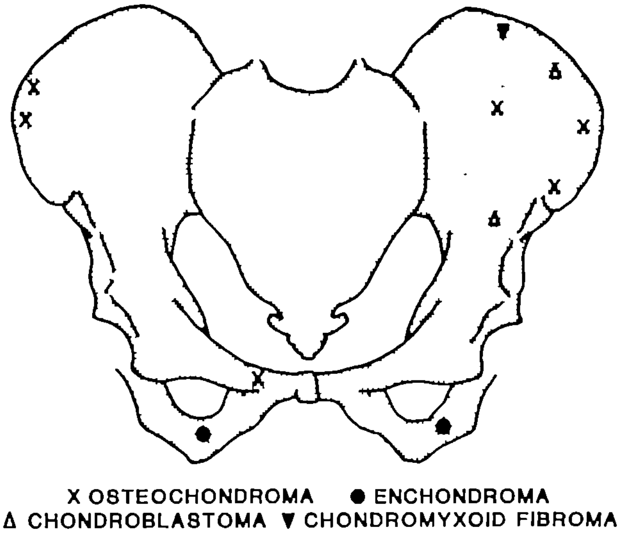
X OSTEOCHONDROMA ● ENCHONDROMA
Δ CHONDROBLASTOMA ▼ CHONDROMYXOID FIBROMA

FIG 2.

Distribution of benign tumours. The osteochondromas occur mainly around the iliac crest. Chondroblastomas arise in previous apophyses.

asymptomatic. The history was unknown in the eleventh.

The distribution of tumours around the pelvis is shown in Fig. 2. No benign tumour was found in the sacrum. The commonest lesions were osteochondromas (54%), which arose around the iliac crests and the pubic rami. Radiologically, these were typical, the cartilage caps containing well defined curvilinear calcification (Fig. 3). One patient had diaphyseal aclasia, the osteochondroma presenting in the pelvis being considerably larger than in any other similar tumour in this group (Fig. 4).

Two enchondromas were identified, both arising from the inferior pubic ramus in a metadiaphyseal position. Radiologically, the lesions appeared purely lytic with slight fusiform expansion of bone, endosteal thinning of cortex and a well defined zone of transition without a sclerotic margin. Calcification was not detected within the tumour, nor was there a soft-tissue mass. The two chondroblastomas arose at sites of previous apophyses. Radiologically, they appeared as well defined radiolucencies with sclerotic margins, exhibiting cortical thinning and slight expansion of bone. No calcification was seen within the lesion, although trabeculation was prominent within the iliac case (Fig. 5).

The distinction between chondroblastoma and the single case of chondromyxoid fibroma was radiologically very difficult. The latter produced a lytic lesion at the same site as a chondroblastoma but there was no expansion of bone and the endosteal margin was markedly irregular and sclerotic. Again, no lesional calcification was detected.

Malignant tumours (29 patients)

These lesions fell into two groups: 20 chondrosarcomas (CS) and nine chondroblastic osteosarcomas (COS). Although COS were less common then CS, they represented almost half of all pelvic osteosarcomas in the Bone Tumour Registry. The sex distribution of COS and CS was equal. All patients with CS presented in the age group 25–60 (mean 44) years, whereas half of the patients with COS presented in the age range 10–20 years (Fig. 1). Of the remaining four patients with COS, two arose in areas of Paget's disease. No difference in the symptomatology between COS and CS was discerned, apart from the length of history, which was less than 7 months in all cases of COS, but over a year in 60% of patients with CS. There were significant differences in the distribution of the lesions around the pelvis, CS arising predominantly away from the

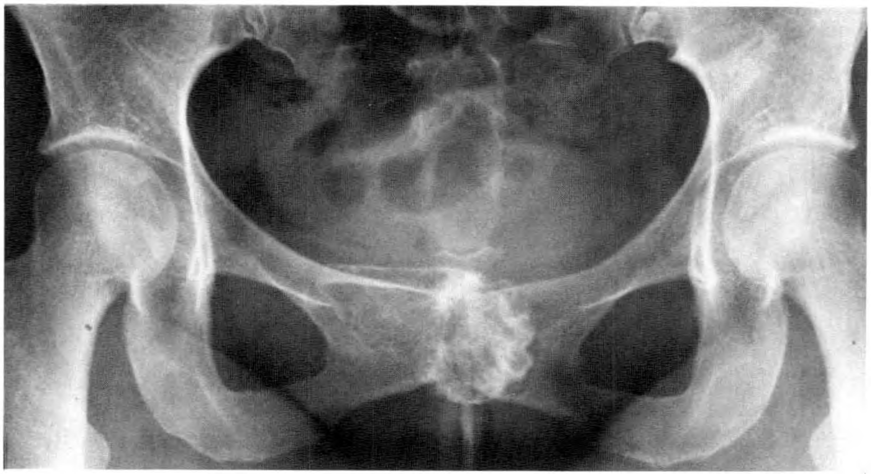

FIG. 3.

Osteochondroma. Well defined calcification is confined to the cartilage cap.

sacroiliac joints, whereas the majority (83%) of cases of COS arose adjacent to them (Figs 6, 7).

Chondrosarcoma and COS had radiologically distinctive features: CS produced two different appearances, depending on the site of origin. The majority (60%) occurred peripherally around the iliac crests and pubic rami, producing a soft-tissue mass of variable size with areas of ill defined curvilinear and amorphous calcification (Fig. 8). Associated bone destruction was seen in both of the tumours which arose in the pubic rami, and in one which arose in the sacrum, but in less than half (44%) of lesions of the iliac blades. The only CS arising near a sacroiliac joint was due to malignant change in an osteochondroma arising posteriorly from the sacral ala.

The second variety of CS (40%) arose in the

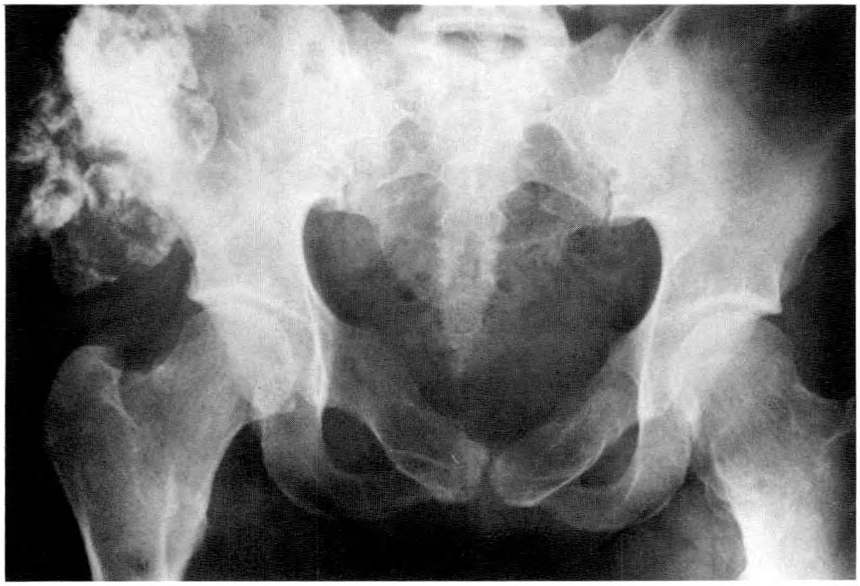

FIG. 4.

Diaphyseal aclasia. Modelling deformities of both femoral necks and superior pubic rami are present. Calcification in the large osteochondroma arising from the iliac crest is still contained in the cartilage cap. No soft-tissue mass or bone destruction is seen.

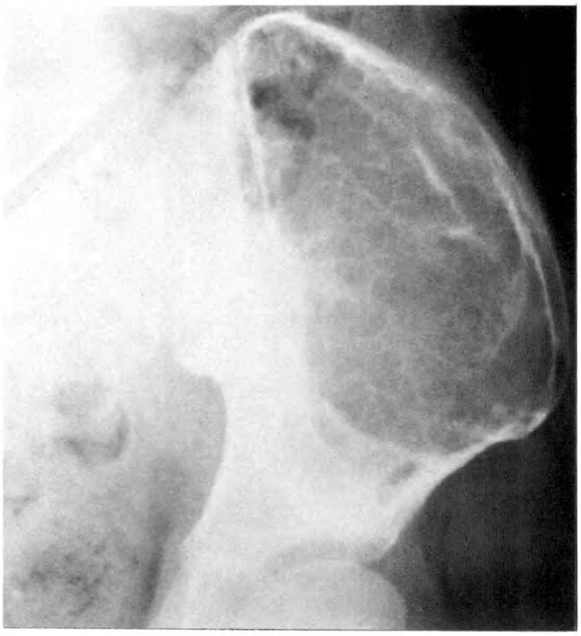

FIG. 5.

Chondroblastoma. A well defined expansile lytic lesion arises from the region of the iliac apophysis. The endosteal margin is sclerotic with trabeculation in the tumour matrix.

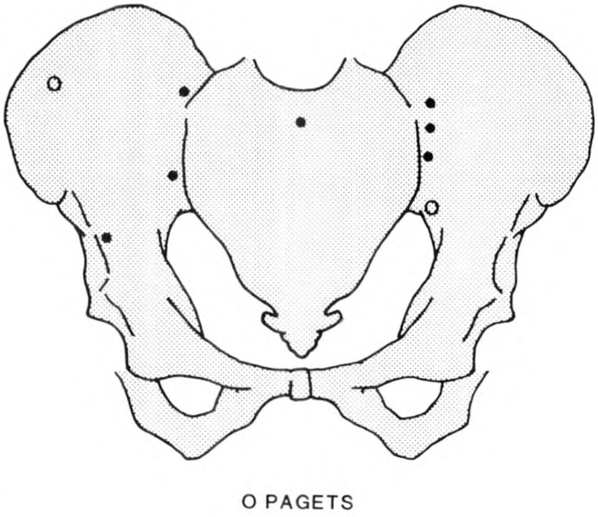

FIG. 7.

Distribution of COS. In five of six patients with lesions unassociated with Paget's disease, these arose adjacent to the sacroiliac joint.

medullary cavity of the floor of the acetabulum at the site of the previous triradiate cartilage. Of seven lesions, six were purely lytic, with endosteal thinning of the adjacent cortical bone (Fig. 9). The larger tumours produced greater expansion and thinning of the overlying cortex. The endosteal margin was usually well defined, although there were areas where the zone of transition was relatively wide. No sclerosis was seen. Calcification within the lesion was detected in one case (14%). One patient had a mixed sclerotic/lytic lesion with linear, radiating calcification within an adjacent soft-tissue mass (Fig. 10). All were associated with thinning or destruction of the acetabular roof and five (71%) had demonstrable soft-tissue masses in the pelvic cavity.

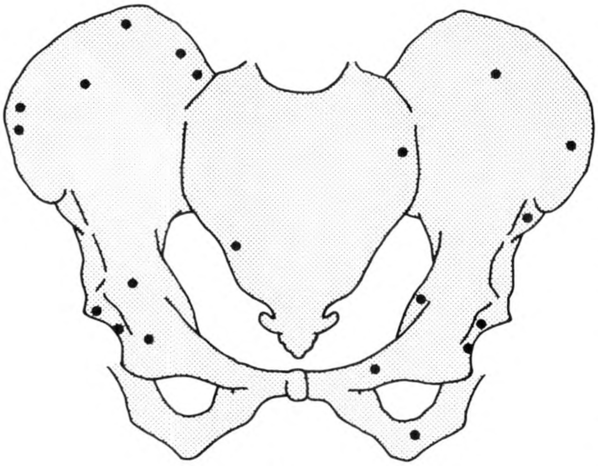

FIG. 6.

Distribution of CS. Two groups are shown, either situated peripherally, around the iliac crest and pubic rami, or centrally around the acetabulum.

Chondroblastic osteosarcoma arose predominantly in the ilium adjacent to the sacroiliac joints. In two, with underlying Paget's disease, COS was identified as ill-defined amorphous sclerosis with effacement of bony trabeculation (Fig. 11). The remaining seven of these lesions produced differing radiological patterns including well defined lytic areas on the iliac side of a sacroiliac joint with destruction of adjacent articular cortex (29%, see Fig. 12), ill-defined sclerosis (42%, see Fig. 13), or mixed sclerosis and lysis with soft-tissue extension (29%, see Fig. 14). Periosteal reaction occurred in one patient in whom a purely sclerotic tumour had extended to the inferior aspect of the ilium (Fig. 13). Both of the purely lytic forms of COS occurred in older patients, whereas sclerotic and mixed patterns were seen in the younger patients. In the one patient with a sacral COS the sclerosis extended across the whole of the sacrum from one sacroiliac joint to the other.

Other imaging techniques

Isotope bone scans were available for six patients and angiographic studies for five. Neither of these

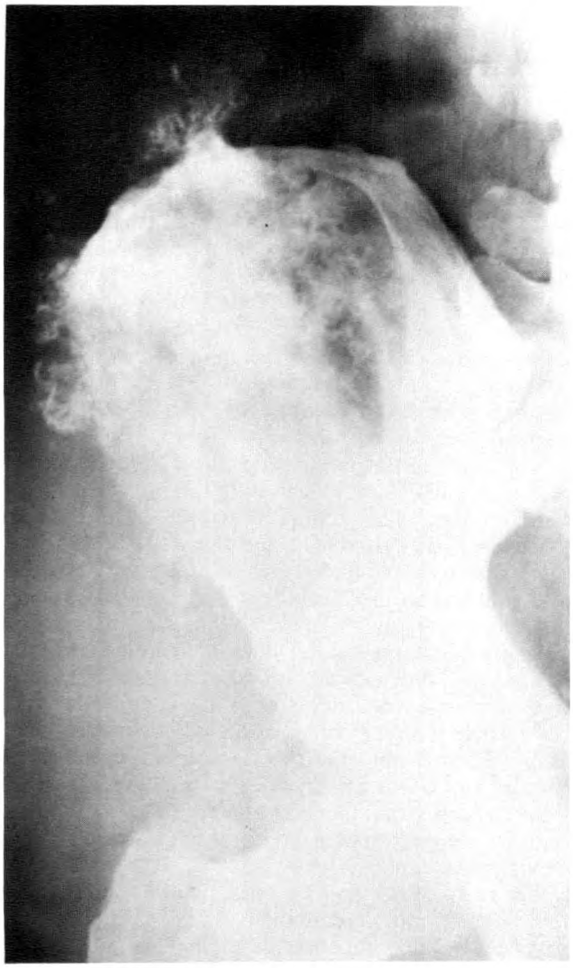

FIG. 8.

Secondary peripheral CS. The soft-tissue mass contains ill-defined areas of calcification away from the main calcified body of the tumour. Destruction of the underlying iliac blade can be seen clearly.

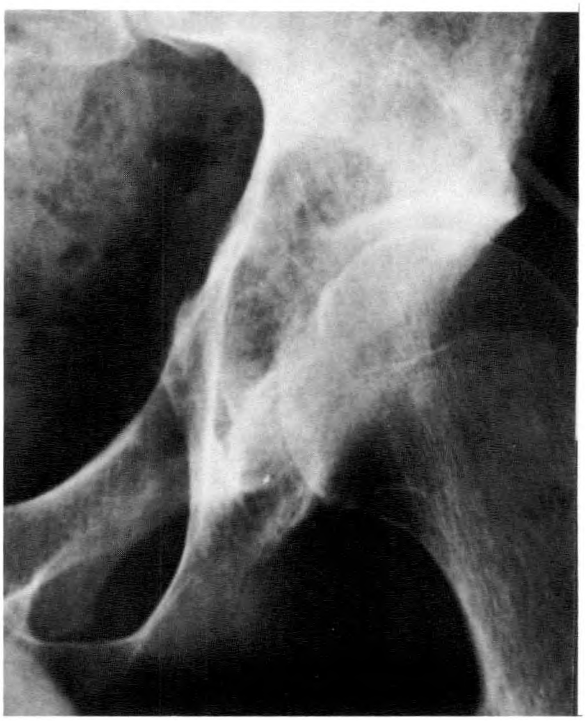

FIG. 9.

Primary central CS. The lytic tumour around the acetabulum is well defined medially but poorly marginated laterally. Thinning and destruction of the acetabular roof has occurred.

techniques was able to discriminate between the various lesions. All the isotope scans showed variable foci of increased activity, while angiography demonstrated differing degrees of vascularity, independent of histological type.

Computed tomography was performed on the last four patients who presented primarily to this centre, all of whom had malignant chondrosarcomas. The intraosseous and extraosseous extent of the tumour and its relationships to surrounding structures were well demonstrated by CT scans, one of which gave clear evidence of bone destruction which could not be seen on plain radiographs (Fig. 15). However, this patient did not have any evidence of calcification within the tumour matrix to enable a specific diagnosis to be made on CT grounds alone. Calcification was clearly seen in the other three patients, supporting the diagnosis of a cartilage-containing tumour. However, there were no features to indicate whether or not the lesion was malignant.

DISCUSSION

It is difficult to gauge why so few examples of benign, as opposed to malignant, tumours are present in the pelvis in this series. Data collected from Tumour Registries are by no means representative of the incidence of disease in the population at large and mainly reflect referral patterns, though the more benign tumours often have few symptoms and presentation occurs because of malignant change, palpable mass or pathological fracture. Furthermore, excision is often undertaken only when malignancy is suspected or the lesion has enlarged sufficiently to cause cosmetic problems.

The radiological characteristics of benign cartilage-cell-containing tumours in the pelvis are typical compared with those of similar tumours seen elsewhere in the skeleton. Osteochondromas, apart from being slightly larger than lesions elsewhere in the appendicular skeleton, have no noteworthy radiological characteristics. Chondromas also produce classical features in the pelvis, although in this series no

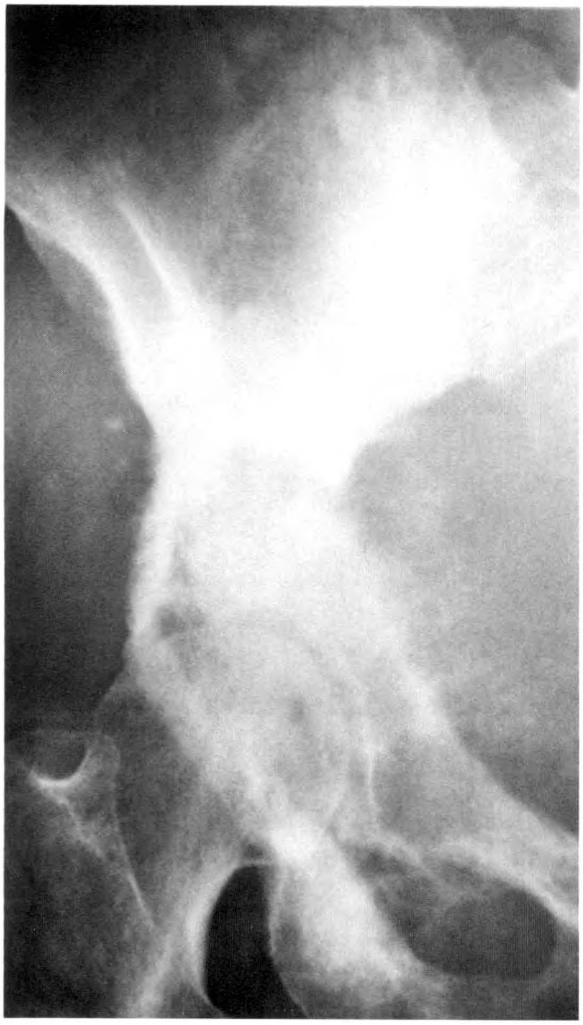

FIG. 10.

Primary central CS. A relatively well defined lytic tumour surrounds the acetabular floor. Prominent irregular periosteal reaction is present with linear calcification radiating into a large soft-tissue mass. The appearances are indistinguishable from those of osteosarcoma.

calcification was present, a helpful sign in peripheral lesions. No difficulty should be experienced in reaching a diagnosis of chondroblastoma, provided attention is focused on the site of origin of the lesion, corresponding as it does to a former apophysis. On the other hand, the single example of chondromyxoid fibroma caused considerable difficulty in diagnosis since its site was atypical, although the irregular sclerotic margin may have suggested the diagnosis.

It is of importance to distinguish between cartilage-cell tumours which are COS and those which are CS (Middlemiss, 1964). The distinction may be extremely difficult to make on purely histological grounds, particularly if an inadequate or unrepresentative biopsy has been performed. Clinically, also, there is little to choose between CS and COS, apart from fact that COS predominates in younger patients and the histories are shorter. Radiological assistance in the differential diagnosis is, thus, valuable and the appearances are sufficient to permit differentiation.

Two forms of CS were observed, although up to four have been categorised (Wilner, 1982) (Fig. 16). The secondary peripheral CS has been shown to arise in conjunction with pre-existing osteochondromas (Norman & Sissons, 1984). This form was the most frequent in the current series, the pattern of distribution closely matching that of benign osteochondromas, confirming a possible relationship. There are very few features whereby secondary peripheral CS can be distinguished from osteochondroma: apart from enlargement in later life and local symptoms, the presence of ill-defined calcification away from the main tumour mass is an important feature of malignancy (Norman & Sissons, 1984), and this, together with the soft-tissue mass and underlying bone destruction, assists in the differential diagnosis.

The other type of lesion found was the primary central tumour, producing lytic areas adjacent to the acetabulum. Previous authors have suggested that this type may arise from the ilium producing lytic, sclerotic or mixed patterns of destruction (Wilner, 1982). However, no example of this tumour was found in the present series, nor of the so-called primary peripheral type (arising from the periosteum) or the secondary central type (malignant transformation in a chondroma).

The radiological diagnosis of a central CS arising in the floor of the acetabulum is extremely difficult, particularly when the observer has not met one before. Several patients in this series had been followed over several months by serial plain radiographs before a biopsy was taken and a definite diagnosis made. The lesion seemed to grow slowly, consistent with the relatively well defined bony margins and expansion of cortex that accompanies it. However, some may become very aggressive (Wilner, 1982), as in one patient in the present series, the appearances being indistinguishable (Fig. 10) from an osteosarcoma. The primary central CS in the floor of the acetabulum poses a wide differential diagnosis. Metastasis usually has a wider zone of transition with earlier cortical destruction. Chondromas, whilst essentially similar radiologically, are predominantly diaphyseal in distribution (Dahlin, 1978). The ill-defined margins may suggest a giant-cell-containing tumour, though few actually arise within the pelvis (Dahlin, 1978). The presence of a sclerotic rim around the margin should raise the possibility of chondroblastoma. Calcification within the lesion is not a useful discriminator.

The features of COS should prevent these tumours being confused with CS, since their distribution is metaphyseal, iliac and adjacent to sacroiliac joints.

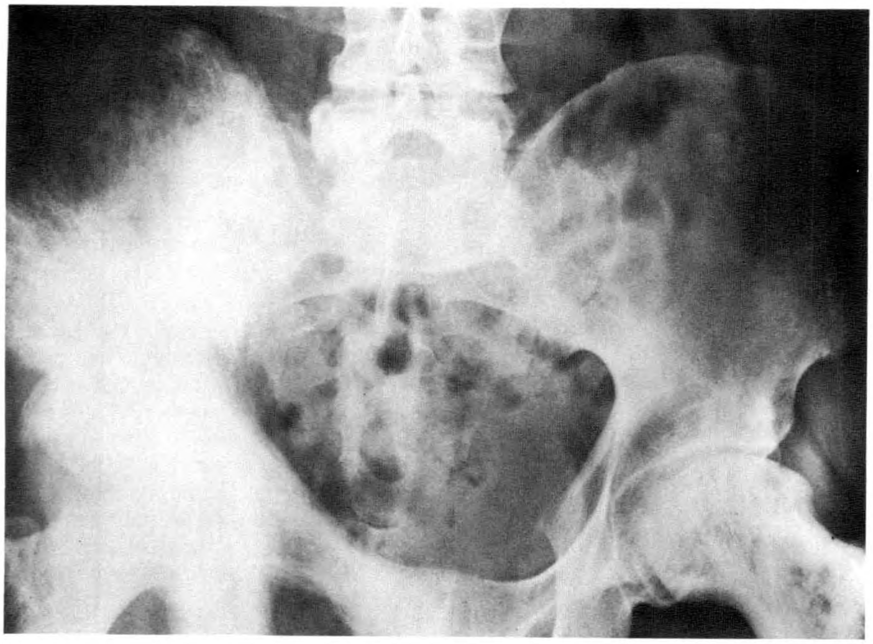

FIG. 11.

Chondroblastic osteosarcoma with Paget's disease. Paget's disease affects the left femur and right hemipelvis. The COS is represented by amorphous sclerosis in the acetabular roof and the medial aspect of the iliac blade.

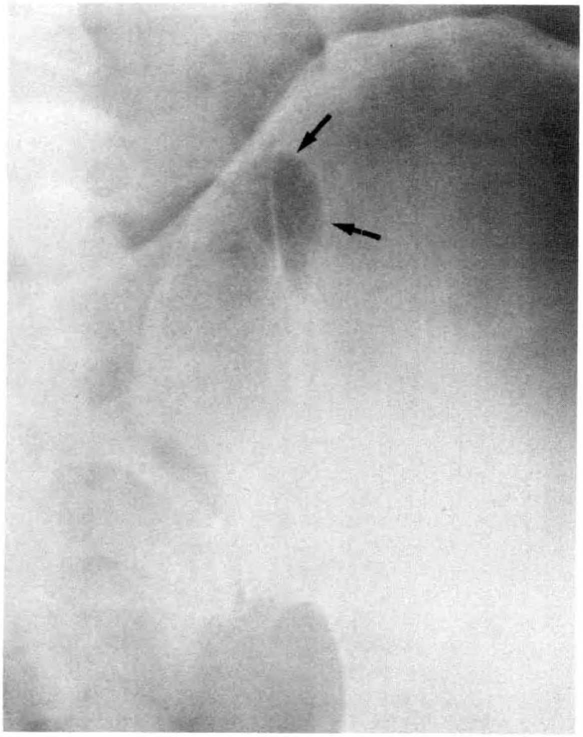

FIG. 12.

Lytic COS. The articular cortex of the ilium at the superior aspect of the sacroiliac joint has been destroyed by a well defined lytic tumour (arrows).

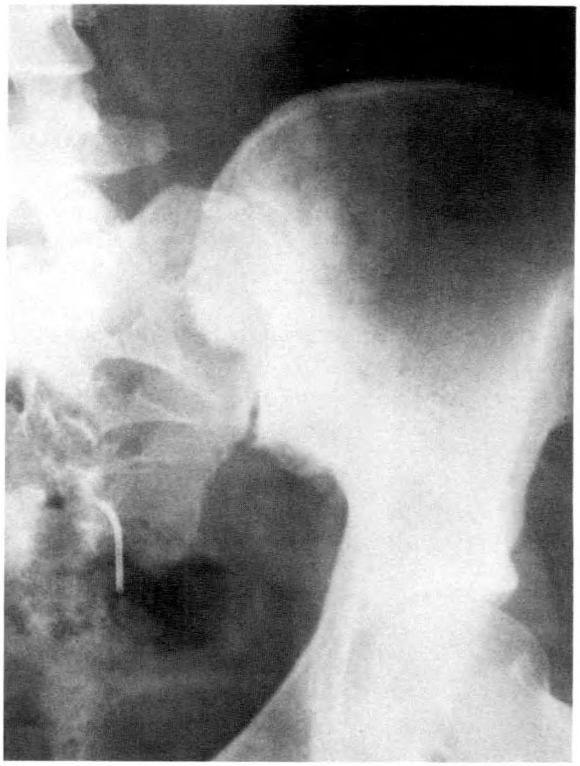

FIG. 13.

Sclerotic COS. Ill-defined sclerosis on the iliac side of the sacroiliac joint extends inferiorly. A small periosteal reaction is present on the posterior aspect of the pelvic brim.

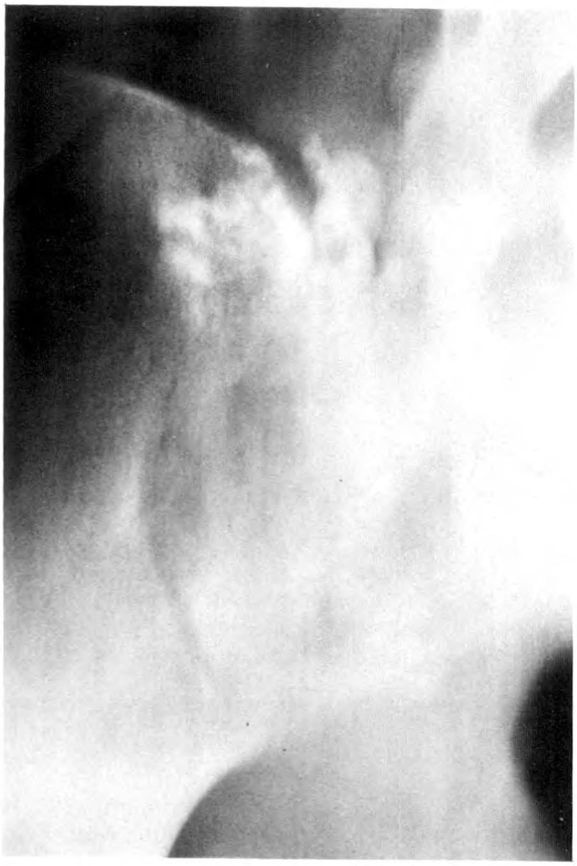

FIG. 14.

Mixed COS. Tomogram showing destruction of the right sacral ala extending to both sides of the sacroiliac joint. Ill-defined calcification can be seen in the ilium and adjacent soft tissues.

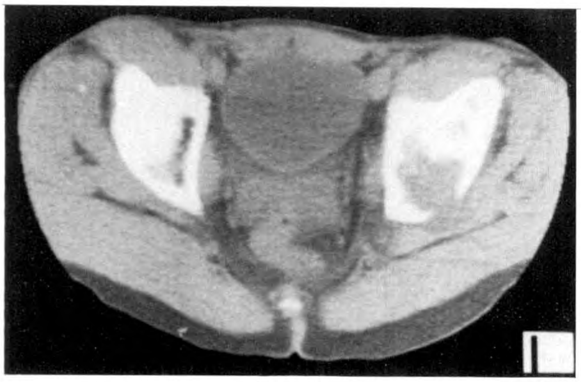

FIG. 15.

A CT scan showing a primary central CS (same patient as in Fig. 9) showing destruction of the posterior column and extension of the tumour posteriorly into gluteus medius (L+20, W 400). Surgical biopsy was made from a posterior approach, thus avoiding tumour contamination of normal tissue.

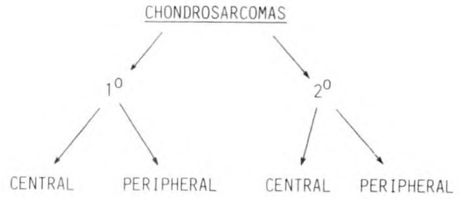

FIG. 16.

Classification of chondrosarcomas (based on Wilner, 1982).

Purely sclerotic tumours, whilst most easily identified, are indistinguishable from other osteosarcomas, radiation-induced sarcomas, lymphomas and metastases. The most difficult lesion to identify is a purely lytic tumour, easily mistaken for overlying bowel gas. However, careful scrutiny will show destruction of articular cortex and adjacent trabecular bone. Lesions with a mixed appearance of sclerosis and lysis should cause no diagnostic difficulty since they are associated with a soft-tissue mass within which calcification or ossification occurs, a characteristic of osteosarcoma in a more typical site.

The role of other imaging techniques has not been explored in detail because in the earlier days of the Tumour Registry these were not available. Indeed, there are still many centres where the plain radiographs remain the basis of patient management. Hence, correct analysis of the radiological appearances is vital and forms the basis of a presumptive histological diagnosis. Computed tomography provides further clinically relevant information, in particular regarding the extent and relationships of the lesion to adjacent structures. It does not provide tumour-specific information or supplant the plain radiograph, but it can provide unique and important information (Fig. 15). Furthermore, CT is ideally suited to the imaging of a complex structure, such as the pelvis. A review of the radionuclide and vascular studies that have been performed showed that they are not capable of discriminating between the various categories of cartilage-cell-containing tumours.

In summary, an analysis of the plain radiographic features should provide sufficient information, in most instances, to differentiate the various cartilage-containing tumours of the pelvis; CT will then provide further information relevant to treatment planning and management.

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Arthrosonography of the irritable hip in childhood: a review of 1 year's experience

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ABSTRACT

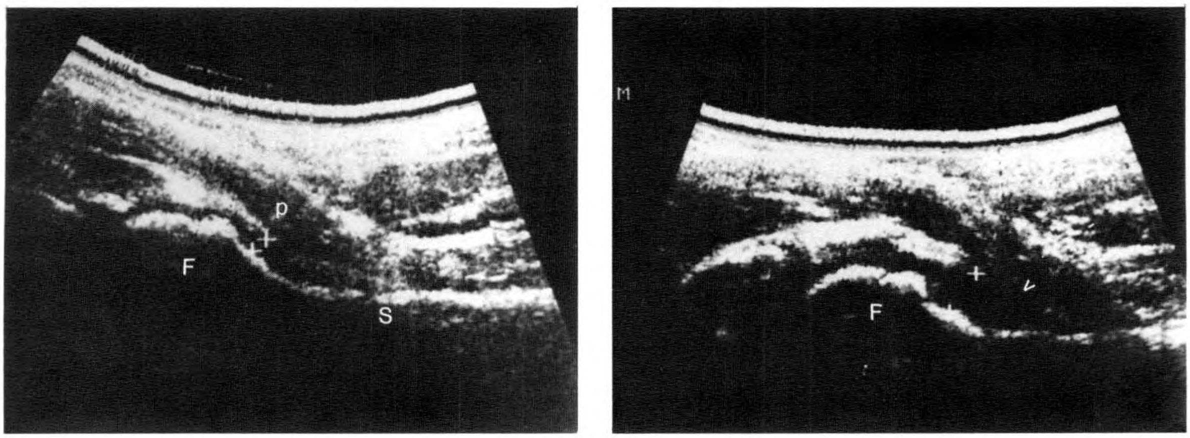
A retrospective study of 87 children presenting acutely with an "irritable hip" was undertaken to assess the role of arthrosonography of the hip joint. Arthrosonography detected 52 hip-joint effusions, of which 16 were aspirated and an effusion confirmed in 14 (88%). In 82 cases plain radiography was compared with arthrosonography for the detection of hip-joint effusions. Of 47 children with a positive ultrasound diagnosis, 28 (59%) showed abnormal findings on plain radiographs and, of 35 cases with negative ultrasound findings, 22 (63%) had a negative diagnosis by plain radiography. Patients with more severe clinical signs were more likely to have an ultrasonic diagnosis of an effusion (87%–100%) than those with mild clinical signs (25%). The ultrasonic measurement of the hip-joint capsule to femoral neck distance was 2.2 mm ± 0.5 mm (mean ± 1 SD) in normal hips and 6.3 mm ± 1.5 mm in the joints with effusions. Our study suggests that arthrosonographically the normal capsular space is less than 3 mm and the difference between the two sides less than 2 mm. It is suggested that hip arthrosonography is a more accurate method for detecting hip-joint effusions than plain radiography; it may help select cases for hospital admission and should be performed before aspiration is attempted.

Arthrosonography has been described as a technique for the investigation of the "irritable hip" in children (Peck & Steiner, 1984).

The technique and anatomical and pathological correlations have been described previously (Armbuster et al, 1978; Seltzer et al, 1980). We have undertaken a retrospective analysis of 87 children who presented with a painful or irritable hip to assess further the value of this technique. This study compared the ultrasonic, radiographic and clinical findings, and also the results of diagnostic aspiration, when performed. The implications for the clinical management of children with irritable hip are discussed.

MATERIAL AND METHODS

Eighty-seven children presenting with irritable hip and 12 normal controls were studied. Those with previously diagnosed hip disease were excluded. Fifty-four male and 33 female patients and six male and six female normal controls were studied. The age range of the children was 3 months to 13 years (mean 5.6 years).



A B

FIG. 1.

(A) Longitudinal ultrasound scan of the left hip showing normal anatomy. F = femoral head, S = femoral shaft, P = psoas muscle, crosses = joint space. (B) Longitudinal scan of the symptomatic hip in the same child. Crosses indicate increased joint space and effusion; arrow indicates inferior margin of the joint capsule.

The clinical assessment of the hip was performed by the Surgical Senior House Officer prior to radiological examination, and was graded as below.

i Pain only, full range of movement (ROM), able to bear weight.
ii Pain, slightly decreased ROM, able to bear weight.
iii Pain, moderately decreased ROM, refusal to bear weight.
iv Pain, no hip movement allowed, refusal to bear weight.

Ultrasonic examination of both hips was done in a plane parallel to, and centred along, the femoral neck. The maximum displacement of the joint capsule from the femoral neck was measured at a standardised position (Fig. 1). A measurement of greater than 3 mm on the affected side, and a difference of greater than 2 mm between the two hips was considered abnormal. These figures were derived from the control group and the normal hips of the children presenting clinically. The psoas muscle can be mistaken for a joint effusion and careful examination is needed to avoid this error.

Most patients were examined using a real-time sector scanner with a 5 MHz probe, and the remainder using a conventional B scanner with a 5 MHz probe.

Standard antero-posterior and frogleg lateral radiographs of both hips were performed within 24 h of arthrosonography. These were interpreted by a consultant paediatric radiologist (M.H.) as showing an effusion to be present or absent with reference to the psoas, gluteus and obturator fat lines, and standardised measurements were made of the distance from the femoral metaphysis to the lateral margin of Kohler's teardrop. A difference of 2 mm or more between the two sides was considered abnormal (Volberg et al, 1984).

TABLE I

COMPARISON OF CLINICAL ASSESSMENT AND ARTHROSONOGRAPHY

Clinical grade		Arthrosonography results	
		Effusion	No effusion
i	(12 cases)	3 (25%)	9 (75%)
ii	(48 cases)	24 (50%)	24 (50%)
iii	(23 cases)	20 (87%)	3 (13%)
iv	(4 cases)	4 (100%)	0 (0%)

RESULTS

Ultrasound

Arthrosonography indicated abnormality in 52 cases and normality in 35 cases. The clinical grades and ultrasound results are shown in Table I.

In the asymptomatic hips of the patients, the mean measurement of the capsule to bone distance was 2.2 mm ± 0.5 mm (mean ± 1 SD), and in the controls 1.5 mm ± 0.2 mm. In the symptomatic hips, the mean measurement was 6.3 mm ± 1.5 mm and the mean measurement on the abnormal side was 4.1 mm ± 1.4 mm greater than on the normal side. Thickening of the joint capsule was seen in two out of five of the children with septic arthritis (Fig. 2).

Aspiration

Diagnostic aspiration was performed in 16 ultrasonically abnormal cases when infection was suspected,

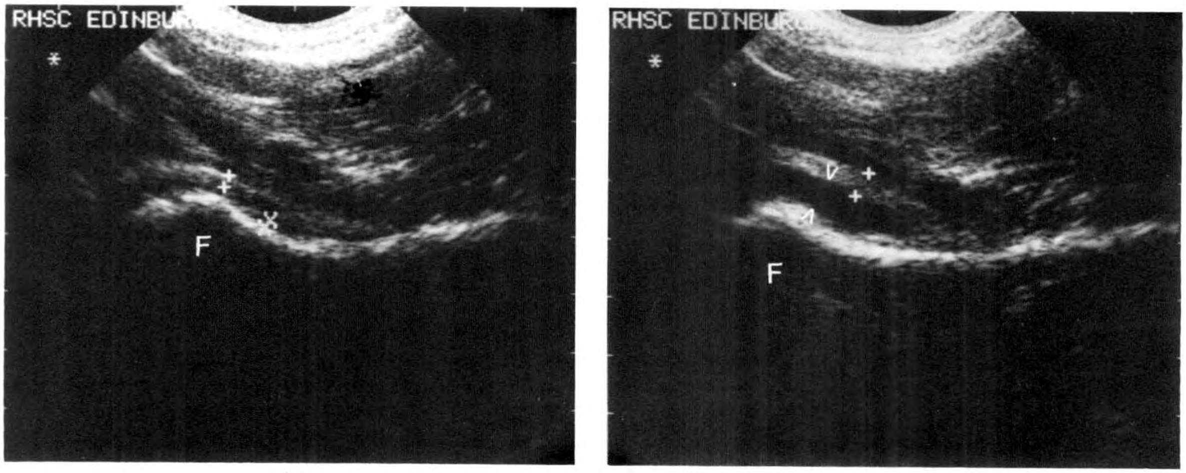


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FIG. 2.

(A) Longitudinal ultrasound scan of the normal hip. Vertical crosses demonstrate normal joint capsule; diagonal crosses indicate the joint space. (B) Longitudinal ultrasound scan of the asymptomatic hip. Crosses show thickened capsule; arrows show joint space with effusion. This child had septic arthritis.

TABLE II

CORRELATION BETWEEN CLINICAL FINDINGS, ASPIRATION AND PLAIN-RADIOGRAPHIC FINDINGS IN 16 CHILDREN WITH EVIDENCE OF HIP JOINT EFFUSION ON ARTHROSONOGRAPHY

Clinical grade	No.	Aspiration findings		Plain radiographic findings	
		Pos.	Neg.	Pos.	Neg.
i	0	–	–	–	–
ii	4	4	–	3	1
iii	8	6	2*	5	3
iv	4	4	–	3	1

*Of the two aspiration-negative cases, one had positive plain-radiographic and the other negative plain-radiographic appearances.

TABLE III

COMPARISON OF RADIOGRAPHIC AND SONOGRAPHIC FINDINGS

Arthrosonography results	Radiographic findings	
	Effusion	No effusion
Effusion total = 47	28	19
Clinical grades		
i	2	1
ii	12	10
iii	11	7
iv	3	1
No effusion total = 35	13	22
Clinical grades		
i	4	4
ii	8	16
iii	1	2
iv	0	0

and fluid was obtained in 14 cases (88%) (Table II). During the 12 months prior to the introduction of hip-joint ultrasonography, our success rate for hip-joint aspiration was only 50% (nine out of 18 cases). Following introduction of ultrasound we aspirated only those hips with an effusion present both on ultrasound and clinically.

Plain radiographs

The comparison of ultrasonic and radiographic findings is shown in Table III. The radiographs for only 82 of the 87 cases were available. Plain radiographs afforded positive diagnoses in 28 of the 47 children with an effusion detected arthrosonographically, and afforded no diagnosis in 22 of the 35 cases where arthrosonography was negative.

The final diagnosis was considered to be "irritable hip" in 75 cases (86%). There were five cases of septic arthritis (all showed effusions) and four cases of osteitis (two femur, one talus, one ilium). Only the femoral osteitis cases showed effusions at arthrosonography. There was one haemarthrosis following trauma, one case which eventually showed evidence of Perthes' disease, and one case where the final diagnosis was of knee pathology.

DISCUSSION

Previous studies have suggested that hip arthrosonography is an accurate method for the diagnosis of hip effusion in both adults and children (Armbuster et al, 1978; Wilson et al, 1984), and our results agree with this.

In the 16 hips aspirated in our series, there were two false positive diagnoses of effusions on arthrosonography and no false negative findings, whereas interpretation of plain radiographs produced five false negative and one false positive diagnoses of hip-joint effusions (Table II). These observations suggest that arthrosonography is superior to the interpretation of plain radiographs in the diagnosis of hip-joint effusion and support previous suggestions that plain radiographs are unreliable in the diagnosis of hip-joint effusion (Volberg et al, 1984; Peck & Steiner, 1984; Rosenborg & Mortensson, 1985). However, several cases of osteomyelitis presented as "irritable hip" and plain radiographs and meticulous clinical assessment remain essential for the diagnosis.

It is not possible to be sure what proportion of effusions are not detected by sonography, since aspiration attempts would be ethically unacceptable in cases with no strong clinical indication. Also, it has been shown in adult hips that 10 ml of added fluid are needed to increase the capsule to bone distance by 2 mm, and 14 ml to increase it to 7–9 mm (Seltzer et al, 1980). It is possible that small quantities of excess intracapsular fluid may not distend the joint capsule enough to be detected by ultrasound.

The small discrepancy between the measurement of the control hips and the asymptomatic hips is probably due to the exclusive use of a machine measuring to the nearest 0.1 mm for the controls, whereas a significant number of the patients were scanned on a machine measuring to the nearest 1 mm. Our experience, using a high quality, modern, real-time scanner with very accurate measuring facilities, suggests that the normal capsule to femoral neck measurement is always less than 3 mm and that the difference between the two hips should not exceed 2 mm.

The thickened joint capsule seen in two of our patients with septic arthritis may be an additional sign for this diagnosis but greater numbers are necessary to substantiate this finding.

Concerning the clinical aspects, a positive ultrasound examination confirmed the hip as the likely cause of the patient's symptoms. In our series, children with fluid in the joint tended to be admitted for further investigation. Clinically less severe cases with negative scans and no other abnormal finding tended to be managed as out-patients. In conclusion, we suggest that ultrasonography should be performed before deciding to aspirate a hip.

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The fractional distribution of the cardiac output in man using microspheres labelled with technetium 99m

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ABSTRACT

To investigate the distribution of organ blood flow in patients we have developed a method of quantitating the whole-body fractional distribution of ^{99}Tc^{m}-labelled microspheres. The microspheres were injected into the left ventricle in nine patients with normal cardiac indices (> 3 l/min/m^2; Group A) and 11 patients with low cardiac indices (< 2.5 l/min/m^2, Group B). The fractional organ content of the total injected dose was estimated following correction for geometry and transmission using a gamma camera. Cerebral blood flow was 579±163 ml/min ($\bar{x}\pm$SD) in Group A and 593±158 ml/min in Group B (p not significant (NS)). Myocardial flow in Group A was 266±82 ml/min and in Group B was 237±57 ml/min (p, NS). Total renal blood flow was 749±161 ml/min in Group A and 614±181 ml/min in Group B ($p < 0.01$). There was a negative correlation between cardiac index and the percentage of the cardiac output distributed to brain ($r = -0.70$, $p < 0.01$), heart ($r = -0.67$, $p < 0.01$) and kidneys ($r = -0.47$), $p < 0.05$). Low output cardiac failure is, therefore, associated with relative preservation of cerebral and myocardial blood flow and, to a lesser extent, of renal flow. A similar technique using dual labelling would allow an accurate estimation in individual patients, of the change in organ blood flow associated with transient alterations in cardiac output states.

The supply of oxygen is the most important function of the circulation, and complex but sensitive mechanisms ensure the correct regulation of blood flow to each organ during changing conditions. Numerous methods have evolved to study regional organ perfusion blood flow in man. These include measuring trans-organ oxygen consumption, dye and temperature dilution curve, transit time measurement and nitrous oxide and other inert gas-washout techniques (Kety & Schmidt, 1948). All of these methods have theoretical and practical limitations which confine their application to the study of one individual organ at a time. Accurate measurement of regional or total organ blood flow is obtained in experimental animal models using radionuclide-labelled microspheres and the principle of indicator fractionation as pioneered by Saperstein (1948).

The corresponding application of this technique to man has been hindered by a number of problems: specifically the selection of a suitable tracer, quantification of the administered activity and the need for left heart injection. These practical problems have been overcome by the development of bio-degradable human serum albumin microspheres that can be easily labelled and remain stable for at least three hours. This has led to the extensive use of microspheres in delineating patterns of regional perfusion in various human organs following intravenous or intra-arterial injection (Endo et al, 1970; Rosenthall et al, 1966). We have previously presented the results of a study (Freedman et al, 1983) determining organ blood flow in an animal model, comparing ^{99}Tc^{m}-labelled human serum albumin microspheres with ^{46}Sc-labelled carbon microspheres. These data showed a good correlation between the organ blood flows measured by the differently labelled microspheres ($r = > 0.99$, $p = < 0.001$; in the four rabbits studied the average slope of the regression lines was 0.97±0.29). From this study we determined that these microspheres (CIS, TCK-5s) labelled with ^{99}Tc^{m} were suitable for the accurate measurement of organ blood flow in man. In addition, a simplified technique of external quantification of activity contained within an organ using standard nuclear medicine imaging and data processing has been devised (Myers et al, 1981; Lavender et al, 1982). Access to the left ventricle is provided by diagnostic cardiac catheterisation. Thus it is theoretically and practically possible to study organ blood flow in man using biodegradable microspheres according to the principle of indicator fractionation. In this preliminary study we have used this new technique in order to assess the redistribution of perfusion in various organs as an adaptive mechanism in low output states.

PATIENTS AND METHODS

Twenty-two patients were selected from those undergoing cardiac catheterisation over an 18-month period. These patients, 20 men and two women, had a mean age of 51 with a range of 27 to 67 years. Nineteen of them had ischaemic heart disease, two had rheumatic valvular disease and one had idiopathic cardiomyopathy. At the end of routine cardiac catheterisation, when angiography was completed and the patients' haemodynamics had returned to their pre-angiography baseline values, cardiac output was measured using the Fick principle (Selzer & Sudrann, 1958). Immediately after this measurement 4×10^6 albumin microspheres (CIS,TCK-5s, mean diameter 15 μm, range 7–25 μm) labelled with approximately 370 MBq (10 mCi) ^{99}Tc^{m}, which had been repeatedly sonicated, were injected into the apex of the left ventricle through a No. 8 pigtail catheter over a period of 20 s. During the microsphere injection no significant changes were observed in the patients' heart rate, mean arterial pressure or electrocardiogram. The catheter was then removed and with haemostasis ensured in routine fashion, the patient was transferred to the Nuclear Medicine Department.

For each area of interest a series of five 1-min images was acquired using a large-field-of-view gamma camera (IGE 400T) interfaced to a dedicated nuclear medicine computer (MDS A^2). The following sequence of imaging was performed:

(a) An anterior emission image with the photopeak energy at 140 keV and a 20% energy window setting for ^{99}Tc^{m};

(b) an anterior emission image with the photopeak energy set at 122 keV for the ^{57}Co transmission source;

(c) an anterior transmission image with the ^{57}Co source held beneath the patient and using the ^{57}Co photopeak setting;

(d) a posterior image obtained with the photopeak energy setting for ^{99}Tc^{m} after rotation of the camera through 180° and repositioning to image the same area.

Following repositioning of the patient this series of successive images was repeated such that the whole body was covered in four or five positions

(e) A flood field image was acquired using a ^{57}Co source held below the couch without the patient.

The images were checked for alignment and a region of interest (ROI) drawn to circumscribe the image of the organ of interest on the anterior emission ^{99}Tc^{m} image (a). This ROI was then transferred to each of the other images in the corresponding series (b), (c), (d) and (e) and the counts within these regions noted. The actual transmission count value (N_t) is obtained by correcting for the ^{99}Tc^{m} "crosstalk" in the ^{57}Co window by subtracting the counts within the ROI in the emission image (b) from the corresponding transmission image (c).

The absolute activity (A) within a region was calculated from the equation:

$$A = K^{-1} \cdot (N_a \cdot N_p)^{\frac{1}{2}} \cdot (N_t/N_f)^{-\frac{1}{2} \cdot \mu t/\mu e}$$

(Myers et al, 1981)

where μt and μe are absorption coefficients for the transmission and emission sources and K^{-1} is the systems calibration factor which is specific for a particular collimator/gamma camera system, isotope and photopeak window setting determined by a series of measurements on phantoms. N_a, N_p and N_f are the counts in the anterior (a), posterior (d) emission and the flood images (e).

Organ blood flow in ml/min was calculated by measuring the fraction of the total injected activity contained in an organ and expressing it as a fraction of the cardiac output. Whole body recovery was calculated by summation of individual sections and expressed as a percentage of the injected activity. The relative partitioning of cardiac output to individual organs was assessed by plotting organ blood flow, both in absolute values and as a percentage of cardiac output versus the cardiac index. Organ flow values (absolute and % output) were compared in Groups A and B using an unpaired Student's t-test. Regression analysis was performed between values of blood flow to each organ (absolute and %) and cardiac index values. This study was approved by the hospital ethical committee and written informed consent was obtained from all patients prior to the study.

RESULTS

The data from two patients were unsuitable for analysis, in one case due to poor labelling efficiency and in the second case because of errors in the measurement of cardiac output. In the remaining 20 patients satisfactory data were obtained for the following organs: brain, 19; heart, 19; kidneys, 15 and spleen, 17. The missing data points were due to overlap of certain organs in the initial studies performed Cardiac index values ranged from 1.5 l/min/m^2 to 3.7 l/min/m^2; nine of the patients (eight men and one women) had values in the normal range (> 3.0 l/min/m^2) and no evidence of heart failure. The mean values of whole body recovery of the injected dose was 98 ± 11% with a range of 81 to 117%. Fig. 1A shows the whole body distribution of the labelled microspheres in a patient with a cardiac index within the normal range and Fig. 1B the distribution in a patient with a low cardiac index value. They illustrate the poor peripheral muscle perfusion in the low cardiac index group compared to that in the group with values within the normal range.

Cerebral blood flow

In eight male patients with normal cardiac indices the mean value of absolute blood flow to the brain was 579 ± 163 ml/min or 8.6 ± 1.7% of the cardiac output. Assuming the average brain weight in males to be 1400 g, the perfusion of cerebral tissues was 41 ± 11.6 ml/100 g/min. Examination of the values of absolute flow in the whole group of patients shows that there is considerable variation between patients but no significant difference between the absolute levels of flow in those patients with low output cardiac failure (593 ± 158 ml/min) and patients with normal cardiac indices (579 ± 163 ml/min) (Fig. 2). These findings are accounted for by a negative correlation between the percentage of output going to the brain and decreasing cardiac index values in all patients, $r = -0.7$, $p < 0.01$ (Fig. 2).

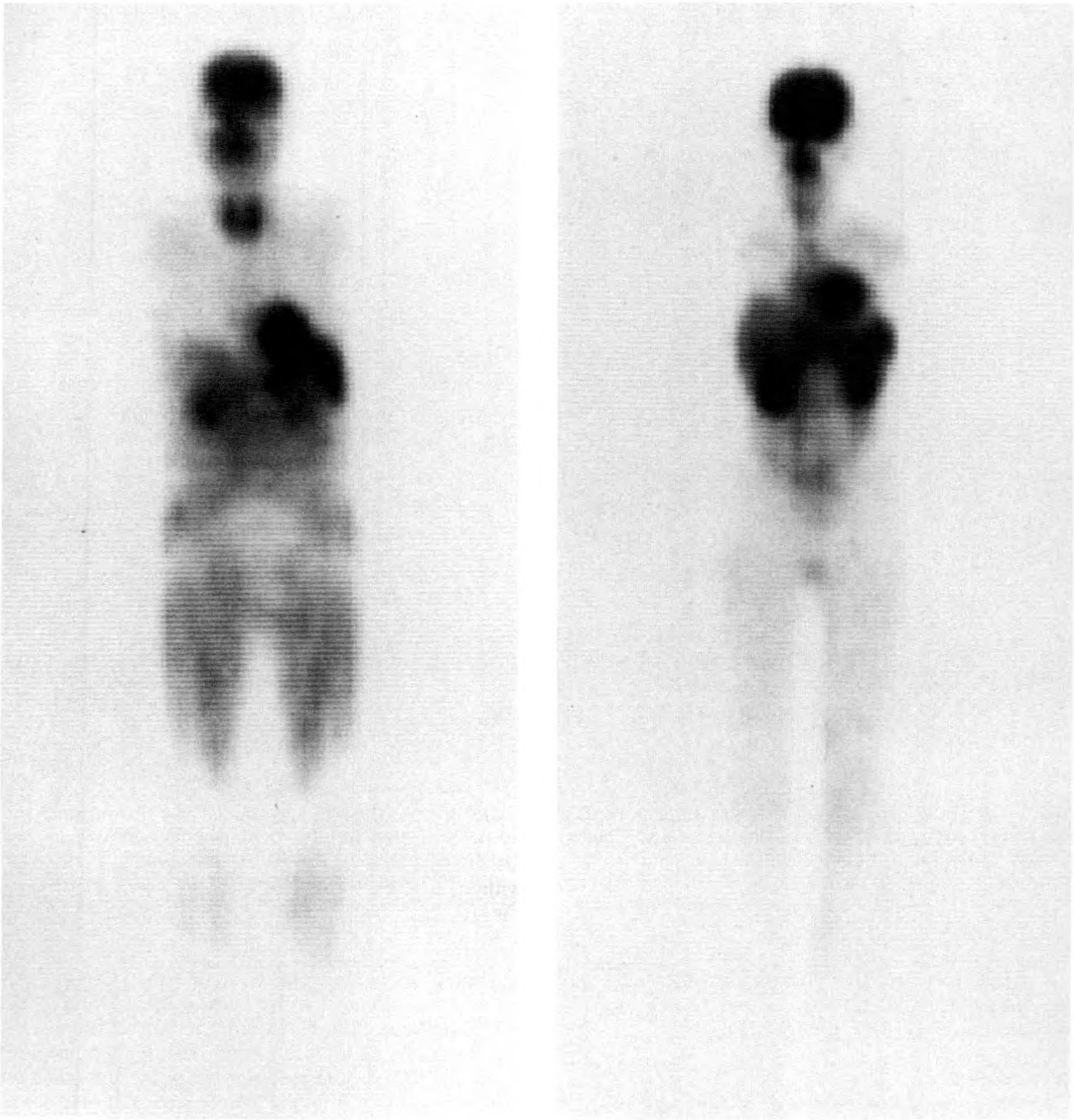

FIG. 1.

Whole body images showing the distribution of labelled microspheres in a patient with a cardiac index within the normal range (A) and a patient with a low cardiac index (B). In both images the central organs are well perfused but only in the patient with a normal cardiac index value can the distribution of microspheres to the peripheral soft tissues be clearly seen.

Myocardial blood flow

The value of myocardial blood flow in nine patients with normal cardiac indices was 266 ± 82 ml/min or 4.3 ± 1.1% of the cardiac output and 237 ± 57 ml/min or 6.3 ± 1.8% of the output for patients in Group B. There was no correlation ($r = 0.12$) between the values of absolute flow and cardiac index. This lack of correlation remained even when flow was corrected for heart size as judged by the chest radiograph or pixel number within the cardiac region of interest. In contrast to this, there

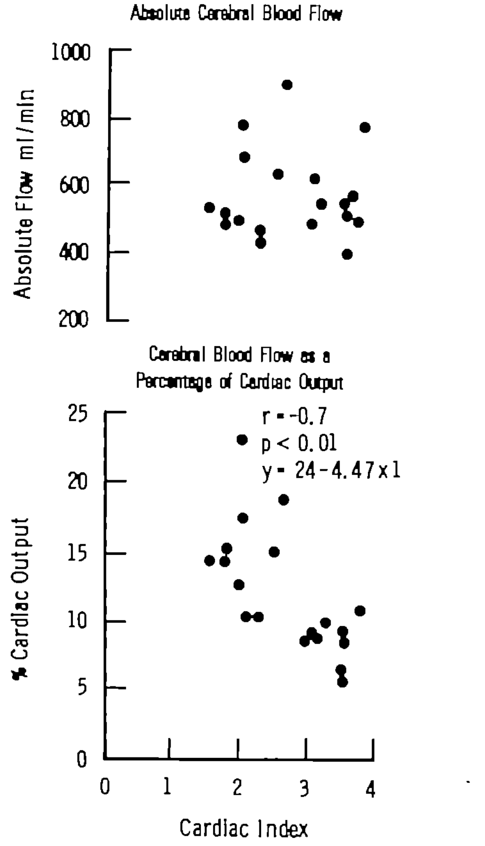

FIG 2

Cardiac index in 19 patients plotted against absolute cerebral flow (above) and against the percentage of cardiac output received by the brain (below) The absolute values of flow show random scatter but there is an increase in the percentage output to the brain with falling cardiac output.

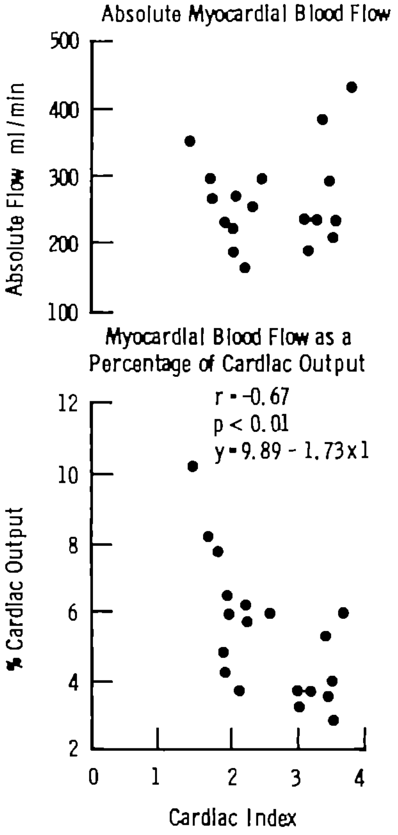

FIG. 3

For 19 patients, absolute myocardial flow (above) and the percentage output distributed to the heart (below) plotted against the values of cardiac output (l/min/m²). Absolute myocardial blood flow is preserved in low output states by receiving a greater percentage of the decreasing cardiac output

was a negative correlation between cardiac index and the percentage of cardiac output going to the myocardium, $r = -0.67$, $p < 0.01$ (Fig. 3).

Renal blood flow

Absolute blood-flow was reduced in patients with impaired cardiac output (614±187 ml/min) as compared with those with normal cardiac indices (759±161 ml/min) ($p < 0.05$). There was however an increase in the percentage of the output going to the kidneys in Group B, 16.4±5% compared to 12.2±3.2% in Group A. The redistribution of flow in heart failure is shown by the correlation between percentage output distributed to the kidneys and the decreasing cardiac index, $r = -0.5$, $p < 0.05$ (Fig. 4).

Splenic blood flow

There was a wide scatter of absolute values of blood flow within the whole group, with no significant difference between the values in Group A, 342±171 ml/min and those in Group B, 303±84 ml/min (Fig. 5). In order to correct for splenic size variation, flow was expressed as ml/min/pixel within the ROI on the posterior image but this failed to alter the scatter of results Patients in Group A received a higher percentage of the output, 9.2±4.1% compared to Group B, 4.7±1.6 in the normal group (p, NS) with a weak negative correlation between cardiac index and the percentage of the output going to the spleen, $r = -0.45$, $p < 0.05$ (Fig. 5).

DISCUSSION

The safety of intravascular administration of albumin particles was first established with their use to image the pulmonary vasculature. Subsequent intra-arterial injections into the renal, coronary and even carotid arteries were not associated with any complications (Endo et al, 1970; Rosenthall et al, 1966). In our study and in a

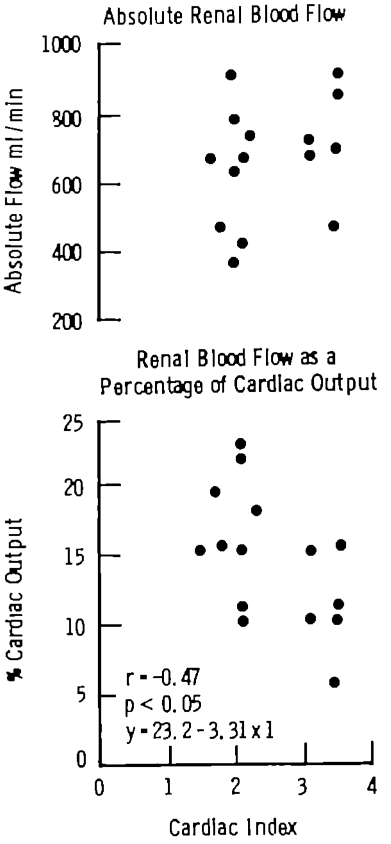

FIG. 4.

Cardiac index in 15 patients plotted against absolute values of renal blood flow (above) and against the percentage of cardiac output received by the kidneys (below). Although there is a compensatory rise in the percentage output distributed to the kidneys as the cardiac output falls, it is insufficient to maintain absolute flow values in those patients with low output states.

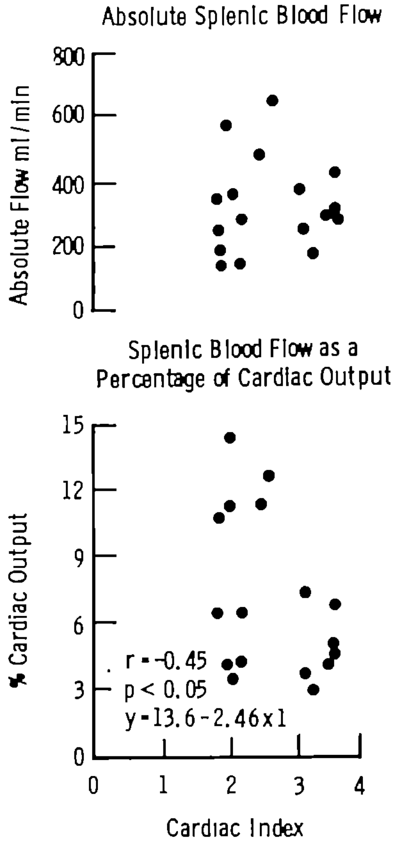

FIG. 5

Splenic blood flow, absolute (above) and as a percentage of the cardiac output (below), plotted against cardiac index values in 17 patients. The scatter of absolute values of flow is similar in both low and high output states with only a weak inverse relationship between falling cardiac output and the percentage of output going to the spleen.

similar study of 14 patients, no changes in either the haemodynamic or electrocardiographic parameters were seen during or following the microsphere administration (Bencivelli et al, 1980). This safe record is ensured by random microscopic examination of particle size and attention to detail to avoid clumping during preparation and prior to injection.

Potential errors in the study

The application of the principle of indicator fractionation implies certain prerequisites. These include thorough mixing of the tracer proximal to the site of its total extraction on first pass and stability of the chosen tracer following impaction for the duration of the study. Although, theoretically, intra-atrial injection may be required to ensure good mixing, Buckberg et al (1971) demonstrated, in a series of animal experiments that, provided more than 400 spheres are contained in the sample counted, exactly similar results were obtained with intra-atrial or intra-ventricular injection. Our data showing no intra-patient variation greater than ±12% between right and left renal flow also supports the concept of good mixing following intra-ventricular injection of the spheres, as further mixing is unlikely to occur in the laminar flow system of the aorta. The stability of the label during the period of the study may be seen by the virtual constancy of counts in a region of interest during the study and the lack of accumulation of isotope in the thyroid and stomach as might be expected from free $^{99}Tc^{m}$ which could leak from the microspheres.

The other possible sources of error in this technique include counting errors, assumptions made in the formula for the derivation of activity from counts in a region, assignment of the ROI and measurement of the cardiac output. Statistical counting errors were low, below 5%, due to the high count rate in each region. Phantom studies with this method, using a range of volume sources in varying depths of water, demonstrated a total quantitative error in the calibration factor of ±6% (Myers et al, 1981). Unlike phantom experiments where the source lies in an isotope-free bath, our measurements of activity in an organ will also include activity arising in the tissues above and below the organ of interest. Thus our values of flow will include an overestimation, albeit small, for all organs in the study. The choice of ROI for a specific organ will involve some error because of the limited resolution of the camera, although with the high target-to-background ratio achieved this error should be minimal. The last source of error arises from the measurement of the cardiac output with the Fick principle, but should be within ±9% (Selzer & Sudrann, 1958). The effect of these compounding errors suggest the total accuracy should lie within ±16%.

Cerebral flow

The value of cerebral blood flow rate in eight men in our series with normal cardiac output was 41±11.6 ml/100 g/min. This is similar to the values of 45 ml/100 g/min, calculated by Saperstein and Ogden (1956) and later Lassen and Klee (1965) using ^{85}Kr. Veall & Mallet (1966), using the ^{133}Xe wash-out technique following inhalation, estimated that normal cerebral blood-flow was 40 ml/100 g/min. Our results demonstrate maintenance of flow despite falling cardiac output. This is similar to the conclusions of Sensebach et al (1960) and Eisenberg et al (1960) who noted a decrease in flow only in very severe heart failure or with decreasing levels of consciousness. The earlier work of Scheinberg (1950) claiming a 39% reduction in cerebral flow seems, as Novack et al (1953) suggested, to be due to comparison of results in heart failure to a normal group rather than to a more appropriate group, similar in age and pathology but not in heart failure.

Myocardial flow

Measurement of total myocardial blood-flow in man has not previously been performed. The extrapolated values of total flow, using O_2 consumption, of 250 ml/min or 4.7% of the cardiac output is similar to our result of 266±82 ml/min or 4.3±1.1% of the cardiac output in normal output states. The other techniques of measuring myocardial blood flow, thermodilution, ^{133}Xe washout, ^{81}Kr^{m} infusion (Selwyn et al, 1978) reflect only regional perfusion. Changes in flow detected by these methods will be influenced by the presence or absence of arterial stenoses in the nutrient artery to a much greater extent than alterations in overall perfusion. Our values of flow in normal output, however, cannot be considered normal values of myocardial flow, as many of these patients had underlying myocardial, valvular, or coronary artery disease.

Renal flow

Renal blood flow, estimated by oxygen consumption in normal humans, is 1260 ml/min or 23% of the output and similar results have been derived using p-aminohippuric acid to measure effective renal plasma flow (Wade et al, 1962). In our study the normal value in six male patients was 759±160 ml/min or 12.2±3.2% of the cardiac output. This low value may be partly due to reduced blood volume induced by pre-catheter fasting and the vasodilatation induced by the use of contrast prior to the measurement. Our values of flow in patients with low cardiac indices 614±187 ml/min are lower than the normal group (759±161 ml/min) but not reduced to one third as suggested by Merrill (1946) and Mokotoff et al (1948). Indeed rather than demonstrating a disproportionate reduction in renal flow compared to the expected fall with a decreasing cardiac output as claimed by those authors, our data suggest preservation of renal flow by a relation between the relative output distributed to the kidneys and the falling cardiac output ($r = -0.5$, $p < 0.05$).

Splenic flow

The value for splenic blood flow in patients with a cardiac index value in the normal range was 342±136 ml/min or 4.8±1.5% of the cardiac output. These values are similar to the previous calculations of flow estimated using ^{111}In-labelled platelets which gave the percentage of the cardiac output going to the spleen as 6% (Peters et al, 1980). The arguments as to whether the spleen is a vascular bed which has different transit times for differing blood cells depending on their size and function is irrelevant to our measurements as the particle size used ensured that all particles were trapped during the first circulation.

As previously reported, the consequence of this autoregulatory preservation of central organ blood flow causes a reduction in the blood flow to skin, muscle, etc. (Wade et al, 1962). Although it was clear from the images in patients with low output that perfusion to the peripheries was poor compared to muscle perfusion in those with normal output states (Fig. 1), we were unable to demonstrate a significant difference in blood-flow to skin or muscle between Groups A and B, mainly due to difficulties in performing satisfactory measurements.

Potential uses of the technique

Our data demonstrate that this technique can be used safely in man to measure, simultaneously, multiple organ blood-flow. We have shown that in patients with heart failure there is a redistribution of the limited cardiac output to ensure a preservation of absolute flow levels to the brain, heart, and, to a lesser extent, the kidneys, consistent with the principle of autoregulation. The possible application of this technique to study blood flow to organs otherwise inaccessible, i.e bronchial and hepatic arterial flow, is of interest to physicians and physiologists. The prospect of using a second labelled microsphere to delineate changes in flow following some intervention is of particular interest to cardiologists. The development of ^{11}C labelled microspheres at our institution offers the possibility of studying blood flow separately from metabolism, using the high resolution of positron tomography (Brady et al, 1983).

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Book reviews

Skeletal Radiography By Sheila Bull, pp. x+213, 1985 (Butterworths, Sevenoaks, Kent), £15.95.
ISBN 0-407-00278-2

I dived into Sheila Bull's *Skeletal Radiography* with anticipation and, indeed, was not entirely disappointed for the book contains a wealth of information on: (a) indications for X-ray examination and (b) the radiographic technique, but this is where I found the book layout irritating as (a) is separated from (b) by many pages

For example, in Chapter 6, there is a full and good account of the pathology of recurrent dislocation of the shoulder, but one has to search further on to find the relevant radiographic projection designed to demonstrate the hatchet deformity so described.

Once located, radiographic techniques are usually well described and there are some helpful line drawings.

At £15.95, the book is relatively inexpensive and, I imagine, aimed at the radiographer working in a general X-ray department who may occasionally be called upon to undertake unusual projections to demonstrate a particular lesion: if so, the book *cries out* for more radiographs. It is of little use to describe a projection without a radiographic example.

Sheila Bull has tackled the long-overdue task of linking skeletal pathology and its imaging in an affordable book and, as such, it should find its way onto the shelves of radiographic schools. Practising radiographers, however, will lament the lack of illustrations and I know would be prepared to pay the extra required to see the radiographs.

J. A. SMITH

A Practical Approach to Modern Imaging Equipment. 2nd Edit. Ed. by T T. Thompson, pp. xviii+336, 1985 (Little, Brown & Co., Boston Mass.), $24.95.
ISBN 0-316-841943

The title of this second edition has been changed to embrace computed tomography, magnetic resonance imaging, nuclear medicine, and ultrasound equipment. The basic underlying concepts which relate to the equipment application are described with emphasis placed upon those topics which relate more directly to currently available technological innovations

The book will appeal to those planning the equipment of departments, besides also being a useful aid to the student by enabling a practical appreciation of some of the practical considerations in the choice of equipment. Mathematical expressions are largely avoided but the reader is, however, constantly made aware of quantitative factors relating to performance and results. The final chapter provides a model purchase specification and a discussion on warranty considerations and maintenance options. Although set in an American context, the counsel of perfection advocated is universally appropriate to the careful choice and specification of equipment prior to purchase.

Most of the writers have been careful to define terms before using them (one exception in Chapter 2 is focal spot bloom, defined in Chapter 3). A glossary of terms would be a helpful inclusion, as the subject area rapidly extends its own jargon.

J. A. GARRETT

1986, *The British Journal of Radiology*, 59, 217–223 MARCH 1986

Persistent sciatic artery. Report of three cases and literature review

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(*Received May 1985*)

ABSTRACT

Persistence of the sciatic artery (SA) is a rare vascular anomaly, resulting from lack of regression of an embryonal artery to the lower extremity. Forty-nine cases have been published in the world literature since 1832. The persistent sciatic artery (PSA) is particularly prone to undergo aneurysm formation or atherosclerosis. It originates from the internal iliac artery, courses in close proximity to the sciatic nerve, and provides the main supply to the popliteal artery because a hypoplastic superficial femoral artery (SFA), contributing only collaterals to the knees, is usually associated with a PSA. This anomaly should be kept in mind in the clinical assessment of a pulsatile gluteal mass. It also presents a potential hazard during hip and renal transplant surgery.

The persistent sciatic artery is a very rare embryological reversion. To our knowledge, only 49 cases have hitherto been published, mostly in the surgical and anatomical literature (Senior, 1925; Mandell et al, 1985; Mayschak & Flye, 1984; McLellan & Morettin, 1982; Youngson et al, 1980; Bower et al, 1977). This atavistic vessel has a propensity to form aneurysms and may present as a pulsatile gluteal mass. Since it is prone to be involved by early atheromatous disease, it may present in the context of lower extremity ischaemia. Some cases have been discovered incidentally during angiography (Wright, 1964). We present two new cases as well as a third case previously reported by our institution (Tisnado et al, 1979). These raise the total number of reported cases to 51. We review the world literature and analyse these cases as well as discussing some of the clinical implications of this vascular anomaly.

CASE REPORTS

Case 1

A 70-year-old diabetic woman was admitted with a history of progressive thigh and calf claudication and right foot rest pain. Arteriography revealed severe atherosclerotic disease in the external and internal iliac arteries bilaterally. A PSA with significant stenosis was noted on the right (Fig. 1). Since a femoral-distal by-pass graft was planned for this patient, percutaneous transluminal angioplasty of a tight stenosis of the right external iliac artery was done preoperatively and resulted in good inflow as determined by postdilatation intra-arterial pressure measurements. Dilatation of the stenosis involving the PSA was considered, but not done since a femoropopliteal graft was deemed necessary. An external iliac-popliteal Goretex graft successfully relieved her symptoms. At surgery, the popliteal artery was found to have a course more posterior and lateral than normal. Postoperative recovery was uneventful.

Case 2

A 33-year-old woman with juvenile-onset diabetes mellitus and end-stage renal disease was admitted for vascular access for haemodialysis. During the previous two years, she had experienced failure of a cadaveric renal transplant in the right iliac fossa, as well as failure of right and left upper extremity Goretex fistulas for haemodialysis. One month prior to admission she underwent another attempt at haemodialysis access by establishment of a Goretex A-V fistula between the distal part of the left SFA and the left greater saphenous vein. Preoperative angiography was not obtained. This fistula failed immediately, requiring haemodialysis through the right common femoral artery and the right common femoral vein.

Angiography was obtained to define the vasculature of the left leg for a planned SFA ligation, fistula removal, and femoro-distal by-pass graft. The angiograms demonstrated a PSA joining the popliteal artery distal to the occluded graft (Fig. 2). Thus a graft removal without the need of a femoro-distal bypass was easily performed.

Case 3

A 42-year-old woman with a three-month history of sciatic-like pain in the right lower extremity was admitted for assessment. She had previously undergone a lumbar laminectomy without relief of her pain. She denied lower extremity ischaemic symptoms. Physical examination revealed a 4 × 5 cm firm, pulsatile, non-tender mass in the right buttock. An aneurysm of the right inferior gluteal artery was suspected. Angiography showed a PSA with an aneurysm measuring 3 × 4 cm at the level of the greater trochanter (Fig. 3). The patient underwent aneurysmectomy and ligation of the right internal iliac artery. A fibrous sheath separated the sciatic nerve from the aneurysm, which was easily removed without trauma to the nerve. A saphenous by-pass graft was interposed between the common femoral artery and the popliteal artery, which at surgery was found to have a course more posterior and lateral than normal. Recovery was uneventful without evidence of vascular or neurological compromise.

EMBRYOLOGY

The SA arises from the dorsal aspect of the umbilical artery. It is a branch of the internal iliac artery and the main arterial supply to the lower extremity in the 9-mm

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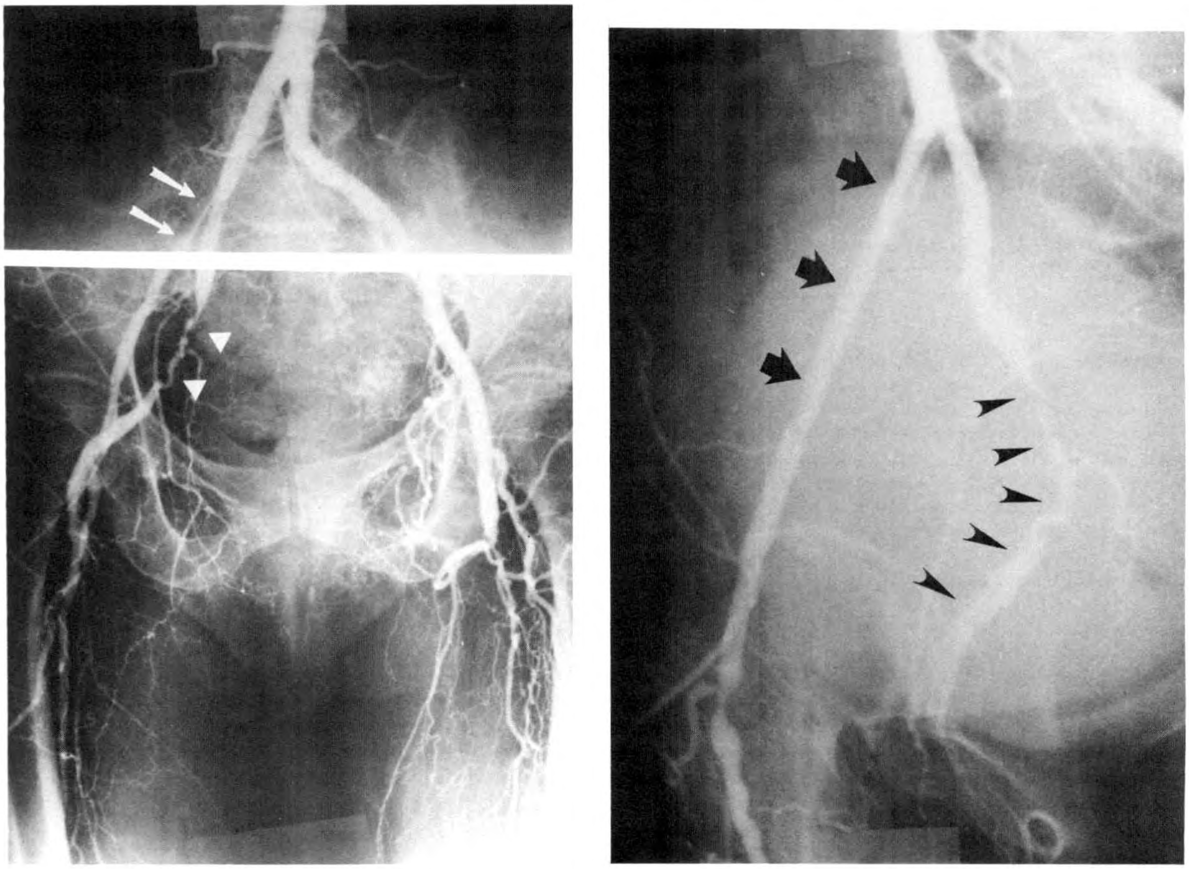


FIG. 1.

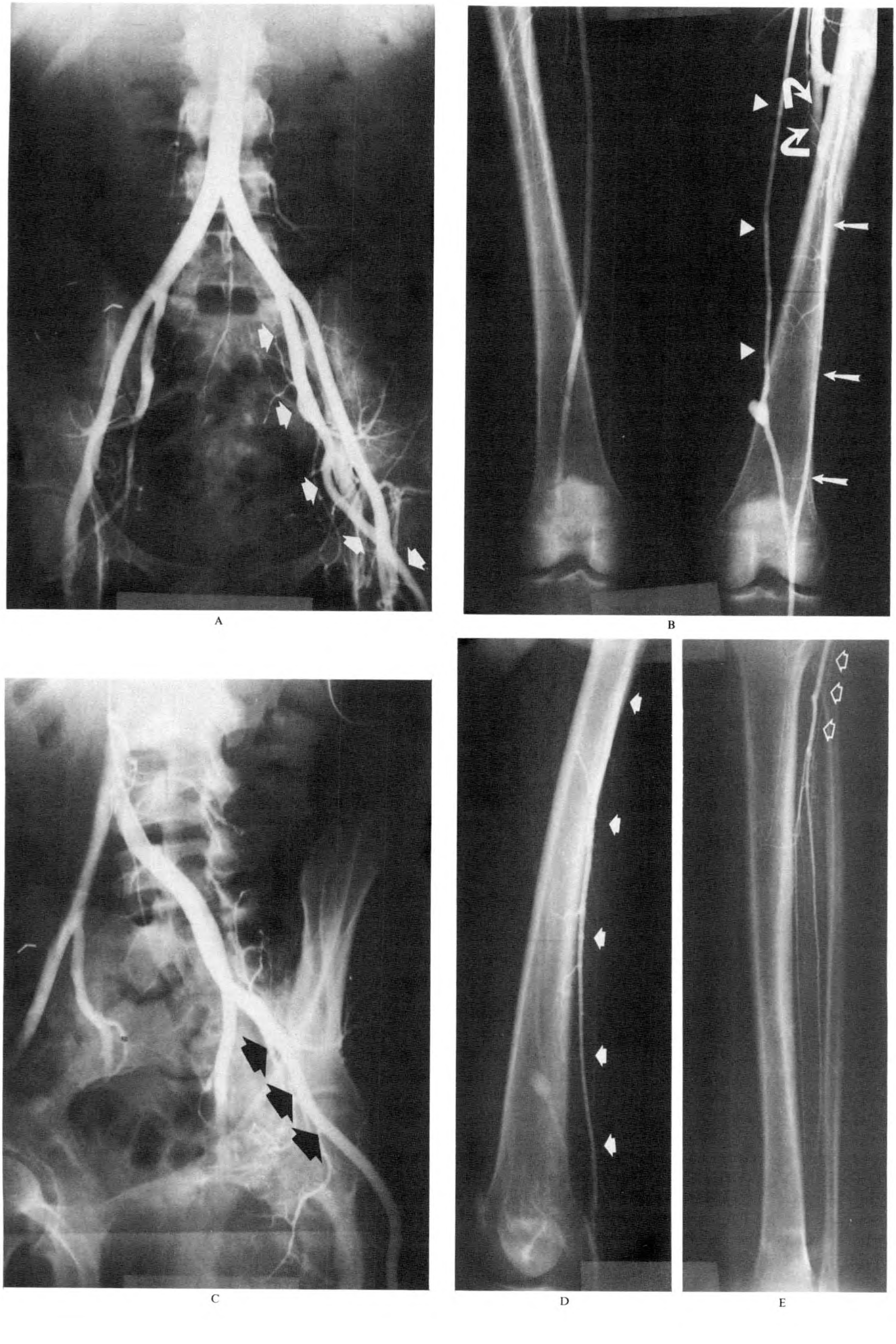
Case 1. (A) Iliofemoral arteriogram demonstrates marked atheromatous stenosis of the proximal portion of the right external iliac artery (arrows). The PSA is much wider in calibre than the external iliac artery. There is a long segment of marked stenosis involving the mid-portion of the PSA (arrowheads) which leaves the pelvis through the greater sciatic notch. The right SFA is occluded, as well as the left superficial and deep femoral arteries. (B) Arteriogram after angioplasty shows excellent dilatation of the right common and external iliac arteries (arrows). The stenotic PSA is well demonstrated (arrowheads).

embryo (McLellan & Morettin, 1982). The SFA originates from the external iliac artery and joins the sciatic artery at the knee. As the blood flow through the SFA increases, the SA regresses. The vestiges of the SA present in the adult include the inferior gluteal artery, a portion of the popliteal artery, and the peroneal artery. Usually the SFA provides the entire blood supply to the leg by the end of the first trimester of gestation.

In patients with a PSA, the SFA is usually underdeveloped distally. It terminates in the region of the adductor canal, forming small geniculate vessels. Its remnant is the posterior tibial artery.

FIG. 2.

Case 2. (A) Pelvic arteriogram in AP projection shows a very large left internal iliac artery continuing into a PSA (arrows). (B) Femoral arteriogram in AP projection demonstrates the left PSA coursing behind the femur (arrows). The left SFA is of normal calibre and course (arrowheads). Both vessels join at the popliteal region. There is partial opacification of the proximal superficial femoral vein (curved arrows). The stump of the failed A–V fistula is noted in the distal portion of the SFA. (C) Selective catheterisation of the PSA in RPO projection demonstrates this vessel leaving the pelvis and coursing adjacent to the greater trochanter of the femur (arrows). (D) The posterior course of the PSA is well demonstrated in this lateral arteriogram of the thigh (arrows). (E) Arteriogram of the left leg demonstrates the more lateral course of the popliteal artery (arrows). An abnormal branching pattern with absence of the posterior tibial artery is noted.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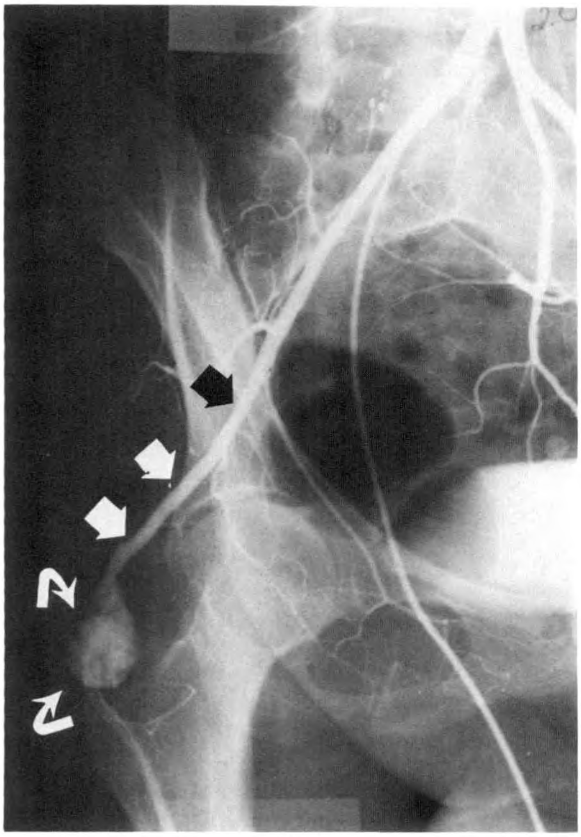

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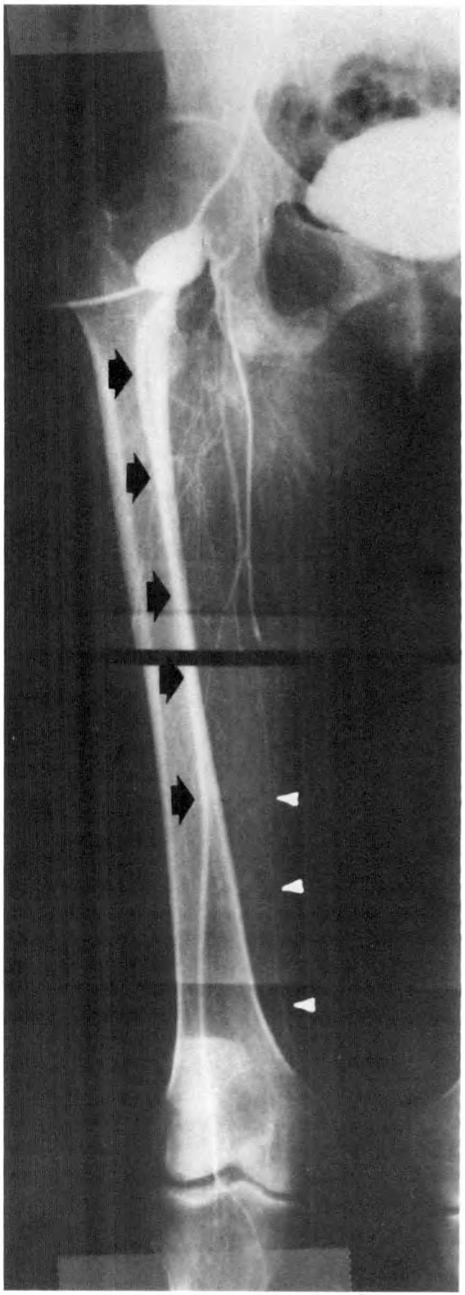

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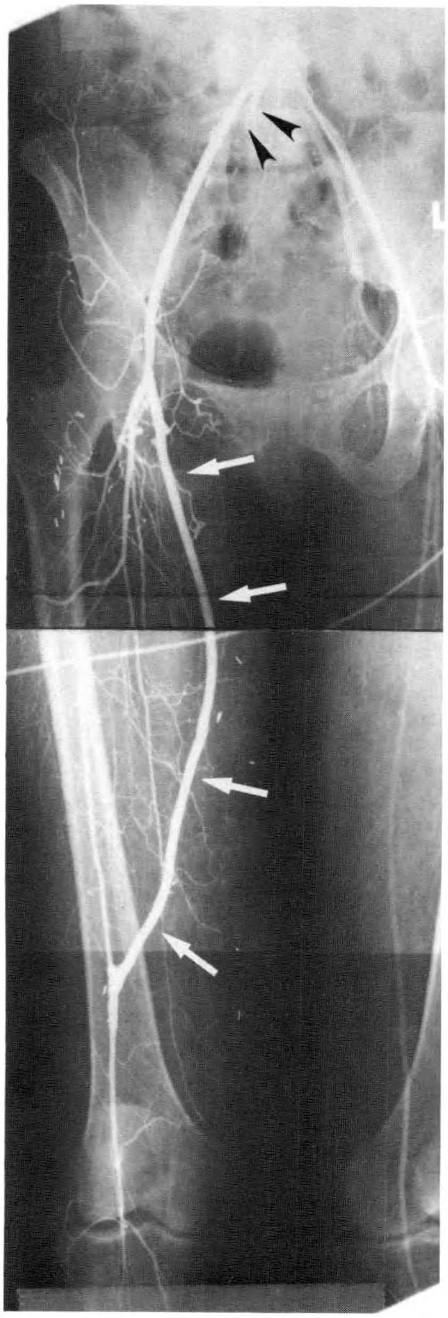
FIG. 3.

Case 3. (A) Pelvic arteriogram in LPO projection shows a large right internal iliac artery continuing as the PSA which leaves the pelvis through the greater sciatic notch (arrows). There is a large aneurysm at the level of the greater trochanter (curved arrows). (B) Right lower extremity arteriogram shows the PSA coursing behind the femur in the posterior compartment of the thigh, joining the popliteal artery (arrows). The SFA is rudimentary and terminates at the level of the knee (arrowheads). (C) Post-operative arteriogram demonstrates a patent femoro-popliteal graft (arrows). The popliteal artery is well opacified proximally (arrowheads). The aneurysm of the sciatic artery is no longer opacified.

ANATOMY

The PSA gives rise to the superior gluteal and internal pudendal arteries within the pelvis, and enters the thigh through the greater sciatic notch, at which point the inferior gluteal artery branches off (Fig. 3). The SA then runs in close proximity to the sciatic nerve and sometimes lies within the nerve sheath. In the posterior compartment of the proximal thigh, it is closely apposed to the greater trochanter of the femur below which it runs lateral to the insertion of the adductor magnus muscle and enters the popliteal fossa to join the popliteal artery, which is consequently displaced somewhat laterally from its usual course. If the calibre of the PSA remains fairly constant from the



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internal iliac artery to the popliteal artery, it is called "complete". If, however, its junction with the internal iliac and/or popliteal arteries is via collaterals it is termed "incomplete" (Bower et al, 1977). In these "incomplete" cases, the SFA often is of normal calibre and continues into the popliteal artery.

LITERATURE REVIEW

The PSA was first reported in 1832 (Green, 1832), and scattered reports have appeared in the world literature since then. Table I was constructed by compiling the data from six summary articles (Senior, 1925; Mandell et al, 1985; Mayschak & Flye, 1984; McLellan & Morettin, 1982; Youngson et al, 1980; Bower et al, 1977) as well as the current three cases, making 51 cases in all. From the table we conclude that the PSA is slightly more common in men, and is more common on the right side than on the left. Usually a complete PSA is accompanied by a hypoplastic ipsilateral SFA. Conversely, an incomplete PSA usually occurs in conjunction with a normal SFA.

Over one-third of the cases have been associated with aneurysms in the region of the greater trochanter, the most likely explanation being the extensive trauma that the hip extensor region receives (Bower et al, 1977). Hypoplasia of the elastic layer of this artery has been postulated as a predisposing cause (Senior, 1925), and may explain why generalised arteriomegaly can occur (Thomas et al, 1978). Three cases have had positive serology for syphilis, probably an incidental occurrence (Clark & Beazley, 1976; Taylor & Fiore, 1966; Joffe, 1964).

Sixteen percent (8/51) of the reported patients have had notable associated physical findings in the lower extremity bearing the PSA. Two patients had lower extremity hypoplasia as well as varicose veins (Nicholson et al, 1977; Cowie et al, 1960); one of these also had neurofibromatosis. Two patients had hemihypertrophy of the affected side (Tisnado et al, 1979; Greebe, 1977) and one of these also had varicose veins and a haemangioma, while the other had an arteriovenous malformation. The remainder had the ipsilateral lower extremity findings of arteriovenous malformation (one case) (Nicholson et al, 1977), varicose veins (one case) (Cowie et al, 1960), "small distal femoral vein" (one case) (Job, 1934), and "crooked legs" (one case) (Bower et al, 1977). It is tempting to hypothesise some disturbance originating in primitive mesodermal structures as a cause for these abnormalities. However, further investigations would be necessary to provide more definitive answers.

DISCUSSION

Persistence of the SA is a very rare occurrence. Greebe (1977) reported two cases of PSA in 8000 arteriograms, yielding an incidence of 0.025%. However, the high rate of aneurysmal formation (38%) of the PSA is noteworthy.

The surgical approach to this vessel in atheromatous disease, with or without aneurysm, is determined by its course through the posterior aspect of the thigh. An interposition graft in the posterior compartment of the thigh would be subject to the same trauma as the original anomalous artery. Mayschak and Flye in a recent article (1984) advocate the use of a femoro-distal bypass graft for the treatment of occlusion of a PSA in a

TABLE I

LITERATURE REVIEW: SUMMARY OF 51 CASES OF PSA

Parameter	Positive/Total (percentage)			
Sex	Male 23/40 (58%)	Female 17/40 (42%)		
Side	Right 19/41 (46%)	Left 9/41 (22%)	Bilateral 13/41 (32%)	
Anatomy of PSA	Complete 48/60* (80%)	Incomplete 12/60* (20%)		
Anatomy of ipsilateral SFA:	Hypoplastic	Absent	Normal	Unknown
complete PSA	41/48* (85.4%)	4/48* (8.3%)	2/48* (4.2%)	1/48* (2.1%)
incomplete PSA	1/12* (8.3%)	1/12* (8.3%)	6/12* (50%)	4/12* (33.3%)
Presence of PSA aneurysm	Greater trochanter region 14/37* (38%)	Generalised arteriomegaly 3/37* (8%)	No aneurysm 20/37* (54%)	
Bypass procedure in cases with aneurysm	Sciatic artery interposition graft 4/17* (23.5%)	Femoropopliteal bypass graft 6/17* (35.3%)	Resection/ligation without bypass 4/17* (23 5%)	No operation 3/17* (17.6%)
Presence of ipsilateral lower extremity abnormality	Varicose veins or small femoral vein 5/51 (10%)	Hemihypertrophy 2/51 (4%)	Shortened lower extremity 2/51 (4%)	"Crooked legs" 1/51 (2%)
	AVM or haemangioma 3/51 (6%)	Neurofibromatosis 1/51 (2%)	Total 8/51 (16%)	
Age when reported: range 0.5–84 years				

*Bilateral cases counted twice. PSA: persistent sciatic artery SFA: superficial femoral artery

symptomatic patient, and for patients with aneurysm formation. Aneurysmectomy has been advocated. However, if an aneurysm occurs within the sciatic nerve sheath, it has been recommended that the aneurysm be ligated but not removed to avoid the risk of nerve injury (Vimla et al, 1981).

Awareness of the presence of a PSA is very important in two special circumstances. Firstly, in hip surgery there is a possibility of trauma to this vessel when the gluteal muscle mass is reflected (Lindenbaum et al, 1978). Secondly, in renal transplant surgery, potentially disastrous limb ischaemia could occur if an anomalous internal iliac artery continuing into the SA were divided and anastomosed to a transplant renal artery (Mayschak & Flye, 1984). The presence of this vessel should be clinically suspected in a patient with an absent femoral pulse and detectable distal pulses. On the other hand, a PSA could be beneficial for a patient such as in Case 2. In this patient, the SFA was ligated and a by-pass graft was not necessary because adequate blood supply was provided to the lower extremity by the PSA.

A stenotic PSA could be dilated by percutaneous transluminal angioplasty if it provided the main blood supply to the lower extremity. In our Case 1, the markedly stenotic PSA did not need to be dilated because the main blood supply was provided by the external iliac and SFA.

Patients with aneurysms of a PSA may present with sciatic-like pain and undergo disc surgery (Case 3). The possibility of this rare anomaly should be kept in mind in such patients if disc surgery does not relieve sciatic pain.

This is a very rare anomaly, and we cannot explain its relatively high incidence in our institution. We have seen three cases in the past five years, performing an average of 500 femoral arteriograms a year. This may be because of increased awareness of the presence of the anomaly.

CONCLUSION

The PSA is a rare vascular anomaly which should be borne in mind in the evaluation of gluteal masses. Because of its course in the posterior aspect of the thigh, the PSA has a propensity to aneurysm formation at the level of the greater trochanter. Also, for this reason, by-pass surgery is best achieved through the femoro-popliteal route. For the orthopaedic surgeon and the renal transplant surgeon, knowledge of this anomalous vessel can avert potentially catastrophic surgical complications.

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Book review

Differential Diagnosis in Conventional Radiology. By Francis A Burgener and Martti Cormano, pp. 740, 1985 (Georg Thieme Verlag, Stuttgart), DM.268.00.
ISBN 3–13–656101–5

Though expensive, this marvellous book is regarded as worthy of an "Oscar" by the registrars in my department. It provides a superb printed film museum, with accompanying differential diagnoses, beautifully presented, with the more common diseases given full emphasis and the less common, such as, Cowden's disease as a cause of polypoid filling defects in the stomach, appearing at the end of the list.

True to the title, the authors have not included any ultrasound, CT or MRI, debating the line that conventional radiographs remain the background of our specialty and remains the imaging method most understood by physicians and surgeons.

The quality of reproduction of the radiographs is outstanding and the images are well spaced, the accompanying table of differential diagnosis being subtly laid out with variations in type emphasis in an attempt to woo the casual reader into reading the entire differential diagnosis.

A candidate preparing for final Fellowship examination would do well to study this book, which would provide a sound revision for the average candidate, yet provide some rich pickings for the high-flyer.

Much of the information is hot off the press, including some radiological features of AIDS. It has an excellent index. Any department preparing candidates for the FRCR or equivalent degree should have one copy on their shelves, though due to the popularity the copy may wear quickly and need to be replaced by another.

R. Dick

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Renal artery stenosis: duplex Doppler evaluation

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ABSTRACT

The renal arteries of 40 patients without renal or renovascular disease were examined with duplex real-time Doppler sonography. Special views were employed to obtain adequate images and Doppler recordings from the renal arteries. Time limits were placed on the duration of the examination, the better to reflect common clinical practice Velocity spectral analysis of the Doppler shift frequency was achieved in 82.5% of the arteries examined and a characteristic "Doppler signature" for the renal artery identified. This was compared with the Doppler signal from the renal arteries of eight patients with renal artery stenosis. Significant differences in spectral pattern were demonstrated in renal artery stenosis. These differences are illustrated and their potential for screening for renovascular disease in systemic hypertension is discussed.

Grey-scale ultrasound, particularly with the advent of high-resolution real-time scanners, has allowed rapid visualisation and characterisation of the intra-abdominal organs with the subsequent identification and evaluation of intra-abdominal disease.

Doppler ultrasound has found application in the evaluation of superficial vessels such as the carotid system and the peripheral vessels of the legs. Simple Doppler systems, however, suffer from lack of range resolution and are, therefore, not routinely applicable to the study of intra-abdominal vessels. The introduction of duplex imaging/pulsed Doppler systems has allowed simultaneous B-mode imaging of the vessel under study, together with the subsequent selection of a sample volume at a particular depth at which to assess the Doppler shift frequency. Such duplex systems have found application in clinical practice, improving the accuracy of carotid vascular diagnosis as well as aiding in the assessment of cardiac disease.

In the abdomen, although there was much enthusiasm in early work, most of the reports have been concerned with the use of Doppler ultrasound to resolve problems of anatomical orientation, anatomical variation or pathological mimicry. Thus, duplex Doppler ultrasound has been used to differentiate dilated bile ducts from vessels (Berland et al, 1982a), cysts from aneurysms and arteries from veins (Taylor et al, 1978; Dubbins, 1984). While these reports clearly identify an occasional role for Doppler during abdominal imaging, no application in the assessment of intra-abdominal pathology has yet been demonstrated. More recent studies have attempted to quantify blood within various intra-abdominal vessels in health and disease, either by assessment of the velocity spectrum or by absolute volume flow measurements (Kossof, 1981; Cole, 1984; Taylor et al, 1985).

Because of its rich blood supply, the kidney is a reasonable model in which to study the potential of Doppler ultrasound for diagnosis. Indeed, several studies suggest a possible role for Doppler in the assessment of the renal transplant (Arima, 1982; Berland et al, 1982; Reinitz et al, 1983).

In the assessment of diseases of the native kidney there are rather more problems related to access. The renal arteries are not imaged routinely on upper abdominal ultrasound studies, although in one study visualisation and Doppler signals from the renal arteries were claimed in 80% of cases (Greene et al, 1981). These workers obtained images of the renal arteries utilising the anterior approach, but up to 1 h was allowed for each examination.

The use of the lateral decubitus view for visualisation of the renal artery has been reported as allowing more frequent visualisation, usually utilising the liver as an acoustic window (*i.e.*, the left lateral decubitus position) (Isikoff & Hill, 1980). It was to evaluate the feasibility of duplex evaluation of renal artery blood flow in a busy ultrasound department using optimum scan planes that this study was undertaken.

MATERIALS AND METHODS

Forty patients presenting to the ultrasound department, Plymouth General Hospital for reasons other than renal or vascular disease were examined The age range was 20–78 years with a sex distribution of 23 women to 17 men. In addition a further eight patients with the angiographic diagnosis of renal artery stenosis, who presented either with hypertension or incidentally during angiographic evaluation of peripheral arterial disease, were also examined. There were four women and four men whose ages ranged between 24 and 62 years. All patients but one were examined after having fasted for 6 h in an attempt to reduce bowel gas using a duplex real-time/pulsed Doppler system with either a 3.5 MHz imaging transducer (3 MHz Doppler) or a 5 MHz imaging transducer (5 MHz Doppler). They were examined at first supine in the longitudinal plane; the aorta and inferior vena cava (IVC) were identified and, where possible, the right renal artery imaged coursing posterior to the IVC. At the level of the right

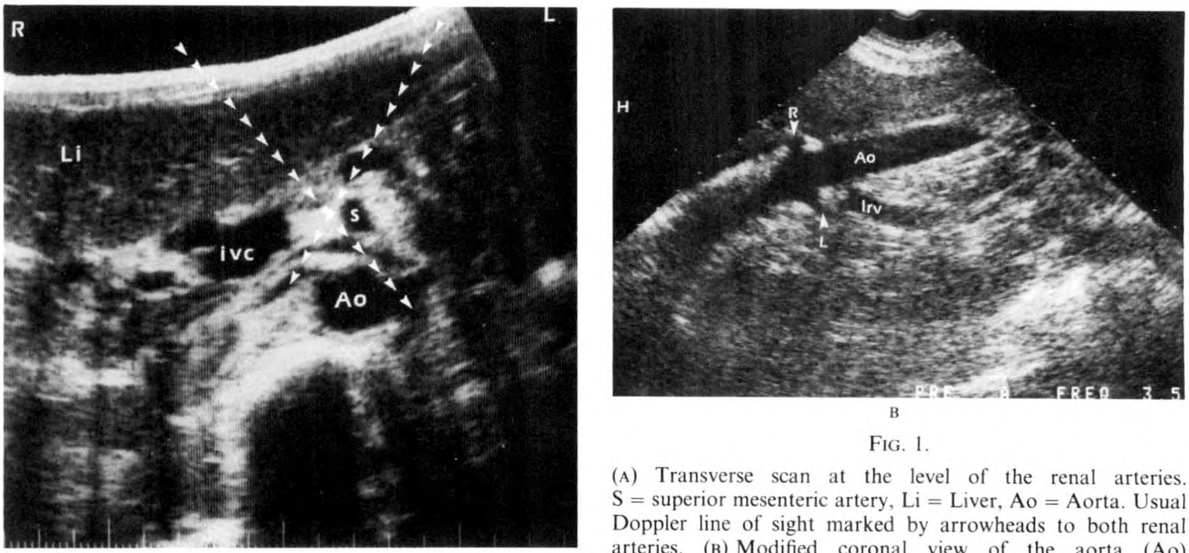

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FIG. 1.

(A) Transverse scan at the level of the renal arteries. S = superior mesenteric artery, Li = Liver, Ao = Aorta. Usual Doppler line of sight marked by arrowheads to both renal arteries. (B) Modified coronal view of the aorta (Ao) demonstrating the lateral branches of the renal arteries, labelled L and R for left and right. A portion of the left renal vein is also demonstrated (lrv).

renal artery the transducer was turned into the transverse plane and the lateral branches of the aorta (*i.e.*, the renal arteries) sought. In order to interrogate the right renal artery the transducer was moved slightly to the left of the abdomen and angulated towards the right to achieve an angle with the vessel of less than 60°. Similarly when seeking the left renal artery, the transducer was moved towards the right side of the abdomen and angled dorsally and to the left (Fig. 1A). The patient was then placed in the left lateral decubitus position (*i.e.*, right side raised). With this approach, a coronal view of the major vessels is obtained (Fig. 1B), allowing more frequent visualisation of the laterally arising renal arteries. The patient was then turned on to the opposite side and an attempt made to visualise the renal arteries. In each case, the line of sight of the Doppler transducer was aligned with the lumen of the vessel under study and the cursor representing the sample volume sited so that it lay within the central portion of the lumen. Minimal sample volume size was used (length of sample volume, 2 mm). The angle was adjusted in all cases to achieve the optimum Doppler signal and, although ideally an angle of less than 60° was sought, accurate measurement of the angle was not always possible. The sample volume was placed within the renal artery within 2 cm of its origin from the aorta. Hard-copy images of the renal arteries were obtained in all planes. Real-time fast Fourier analysis is possible on the particular machine used (ATL Mark 600, Squibb Medical Systems) and spectral analysis of the Doppler shift frequency of each vessel was also recorded on hard copy or videotape. No more than 15 min was allowed for the study and if this time was exceeded without adequate visualisation or Doppler recording then the attempt was abandoned.

RESULTS

The 40 patients examined presented with a wide range of symptoms but predominantly with abdominal pain or suspected gallstones. In the 40 patients, 81 renal arteries were investigated (in one patient two right renal arteries were demonstrated).

Of the 40 "normal control" patients examined, both renal arteries were seen and Doppler flow recorded in 31 (77.5%). In one patient (2.5%) both renal arteries were seen and, although there was audible Doppler on both sides, spectral analysis could be achieved only in the right renal artery and not on the left because of inconstancy of the signal consequent upon respiratory motion. In two patients (5%) the right renal artery was identified and spectral analysis satisfactorily recorded, whereas in one of these patients the left renal artery was not seen nor was a satisfactory Doppler recording made and, in the other, although the left renal artery was identified, no satisfactory Doppler flow could be recorded either audibly or with spectral analysis. In one patient (2.5%) the left renal artery was identified and Doppler flow determined while on the right the renal artery was seen but no Doppler flow recorded. In five patients (12.5%) neither artery was seen and no Doppler flow was recorded.

Of the 81 renal arteries investigated, the total number with recordable Doppler signals was 67 (82.7%). Of the five patients in whom neither renal artery was seen and no Doppler signal recorded, two had acute pancreatitis, one being, in addition, grossly obese, one patient was simply very obese, and one had ptotic kidneys. In the fifth patient there was no clear reason for non-

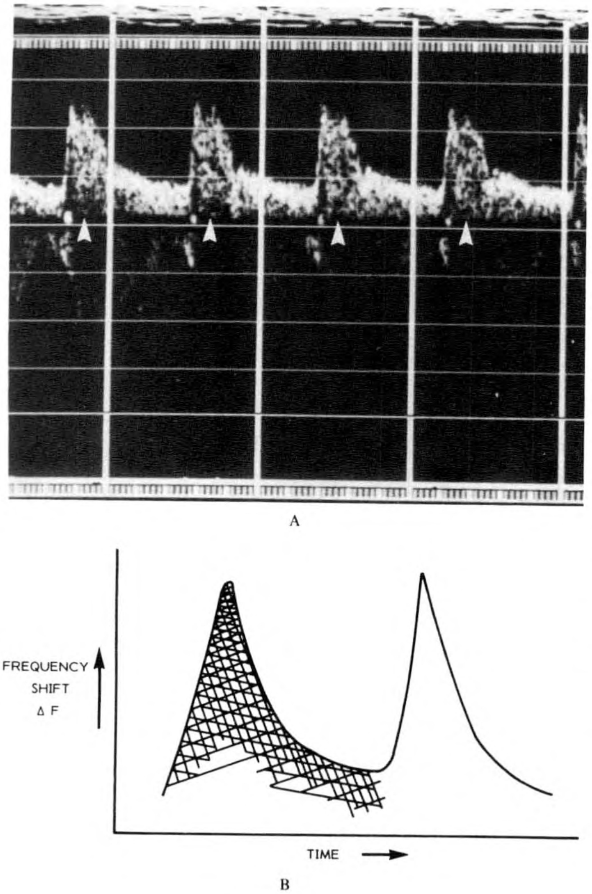


FIG. 2.

(A) Characteristic Doppler signal of a normal renal artery demonstrating the typical "ski-slope" pattern of a low-resistance vascular system. The arrowhead identifies the "clear window" below the systolic element of the spectrum. (B) Stylised drawing of Doppler frequency spectral analysis showing two cardiac cycles. The frequency shift or delta F represents the vertical axis with time corresponding to the horizontal axis. The cross-hatching in the first cardiac cycle represents the spread of frequencies which occur in the renal vessel. These represent the differing velocities of blood flow occurring instantaneously within the vessels.

visualisation of the renal arteries although the patient did have a somewhat scaphoid abdomen.

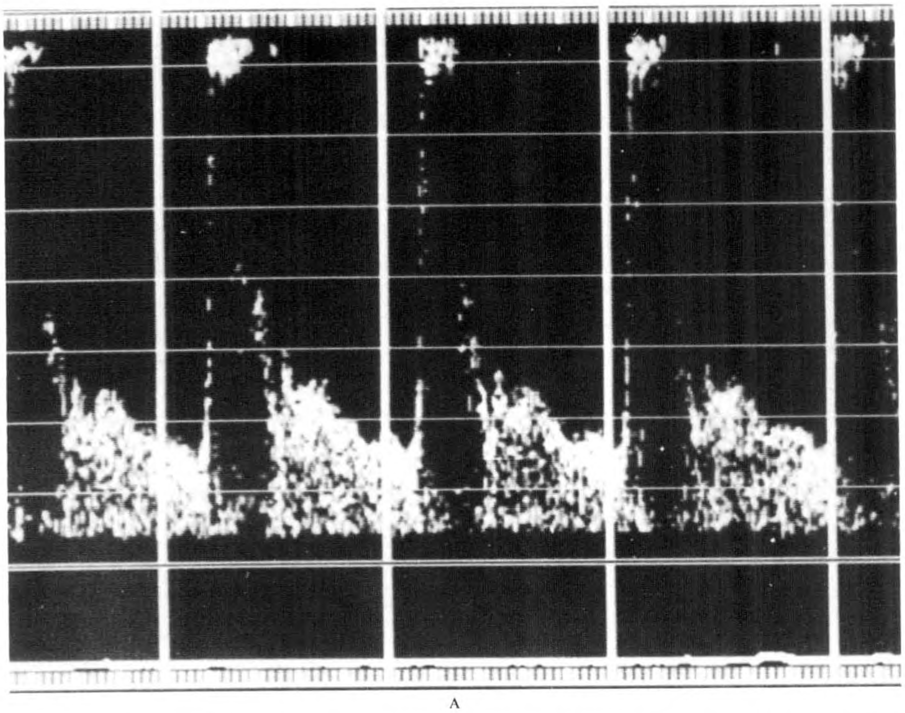
The Doppler signals of both renal arteries were similar and characteristic (Fig. 2), consisting of a sharp upstroke of high velocity in systole with an almost exponential fall to a continuous lower velocity flow in diastole, the curve resembling a "ski slope". There was a clear window below the systolic element of the spectrum. During diastole the spectral envelope showed a relatively wide range of lower frequency signals. Although attempts were made to optimise the angle of incidence of the Doppler line of sight it proved difficult to measure the angle accurately in many cases because, frequently, only a short segment of the artery was identified and its exact course was difficult to extrapolate.

Of the eight patients with renal artery stenosis, seven had unilateral involvement and one had angiographically demonstrable bilateral renal artery stenosis. The results of duplex Doppler investigation in the nine stenotic vessels were as follows. In two patients the stenotic vessel was not visualised by real-time B-mode ultrasound and neither was any Doppler signal recorded. In two patients the spectrum during systole and diastole exhibited increased amplitudes in the lower frequency range, *i.e.*, spectral broadening. These were termed mild/moderate stenoses and were represented by stenoses of less than 50% at arteriography. In the remaining five arteries there was a marked increase in the maximum systolic frequency shift together with significant spectral broadening in both the systolic and diastolic phases of the spectral envelope (Fig. 3). These were termed severe stenoses and were associated with greater than 50% narrowing of the lumen at arteriography. In the two patients in whom no Doppler frequency shift was identified and no renal artery was imaged, the ipsilateral kidney was shown by real-time ultrasound to be small. Both of these patients had over 90% stenosis assessed at arteriography.

DISCUSSION

Pulsed Doppler ultrasound has yet to find a well established role in the investigation of abdominal disease. Although the kidney is a highly vascular organ, the vessels of supply are not easy to image on standard views and may require special techniques for their identification. If Doppler ultrasound is to have a role in the assessment of renal disease then signal recording, processing and measurement must be easy, reproducible and accurate. While in this study only 82.7% of the normal renal arteries investigated produced demonstrable Doppler signals, the presence of acute pancreatitis in a further 5% almost certainly contributed to the non-visualisation of the vessels. Acute pancreatitis is well known to produce small-bowel ileus. This study confirms that the most useful planes of scan, not only for visualisation of the renal artery but also for recording Doppler signals, are the left lateral decubitus (or coronal) scan and the supine transverse scan. If the renal arteries are not identified on these two views then they were rarely identified on any of the others. Visualisation of the renal arteries using these two approaches compares favourably with the results of other workers using the decubitus position (Isikoff & Hill, 1980).

In order to detect accurately changes in blood velocity produced, for instance, by minor stenoses, it is important to investigate the whole Doppler shift spectrum (Reinertson & Barnes, 1976). The wave form of the renal artery is characteristic of a low-impedance system and, although the normal spectrum still shows



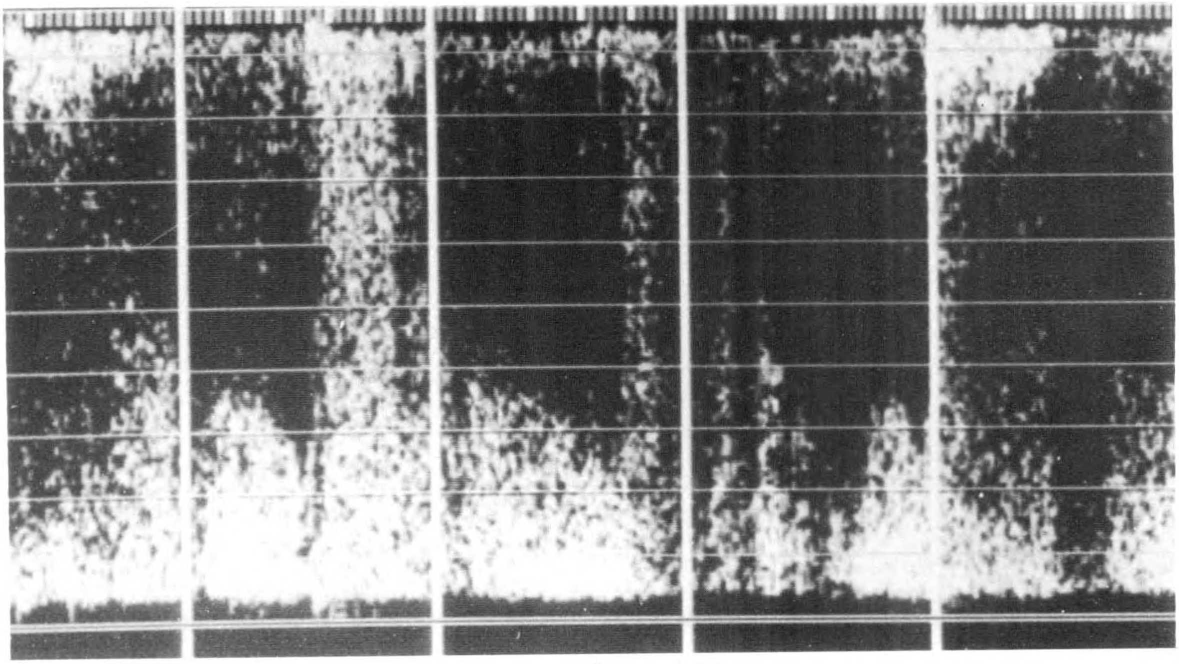


Fig. 3.

(a) Typical spectral pattern of Doppler recording from a renal artery of moderate to severe stenosis with a maximum frequency of Doppler shift of just less than 7 kHz and spectral broadening in diastole. (b) Typical spectral pattern from a patient with severe renal arterial stenosis. The maximum Doppler shift frequency exceeds that recordable by the pulse repetition frequency of the machine. There is marked spectral broadening in both systole and diastole.

the greatest signal amplitude to be associated with the maximum-frequency envelope, this is more apparent in the systolic phase. In the diastolic phase there is rather more spread of signal amplitude (Fig. 2b). Changes in spectral envelope will still occur in response to arterial stenosis but these are likely to be more difficult to quantify because of the wide range of velocities associated with the spectrum of the renal artery, particularly in diastole. In this series, however, it proved possible to identify two grades of severity of stenosis (mild/moderate or severe) on the basis of peak velocity and spectral broadening. These crude gradings correlated with the arteriographic findings. In the assessment of renal artery stenosis with its implications for reno-vascular hypertension this grading may not be important.

In the two cases where there was no recordable Doppler signal and no demonstrable renal artery, it is difficult to draw diagnostic information. While the contralateral renal artery was seen and a Doppler signal recorded in both of these cases, results from the control group clearly show that some 17.3% of all renal arteries may not be visualised. Although in the patients under study the presence of reno-vascular disease might be inferred by the small size of the kidneys this finding was perhaps fortuitous and, if sufficient numbers of patients were examined, a similar failure rate would be expected in renal artery stenoses of lesser severity and without morphological abnormality of the kidney.

While it is clear that there will be a significant number of patients in whom non-visualisation prevents adequate duplex examination, this study confirms the finding of Greene et al (1981), that Doppler, when linked to real-time B-mode ultrasound, can be a useful technique in the assessment of reno-vascular disease. However, those workers used measurements of blood flow velocity and volume flow which depend on the measurement of vessel lumen diameter and angle of incidence of Doppler line of sight to the vessel. The author found these measurements to be both time-consuming and inaccurate. The time limitations placed on the examination of patients were an attempt to provide a realistic approach to a possible clinical role for ultrasound rather than simply as a research tool. It does appear from the study that valuable information about renal artery flow may be provided by assessment of the spectral envelope of the Doppler signal. However, because of the failure rate in normal controls it does not appear possible to suggest that failure to demonstrate a vessel lumen or Doppler flow represents reliable evidence of arterial occlusion as other workers suggest (Greene et al, 1981). In spite of this, it seems likely that Doppler combined with real-time imaging will provide much information about reno-vascular disease.

The demonstration of normal renal artery flow pattern and the alteration of these blood flow patterns by vascular stenosis indicates a possible role for duplex systems within the abdomen. However, renal arterial flow is not affected only by the vessel of supply but also by the physiology and pathology of the end organ. The effect that a low-impedance renal vascular bed has on the characteristic spectral pattern is clearly shown (Fig. 2). Disease of the kidney might also be expected to affect the spectral pattern of the blood flow within the renal artery. We are currently investigating the role of duplex imaging in screening for renovascular hypertension, in renal tumours and in parenchymal renal disease.

ACKNOWLEDGMENTS

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Book review

Radiological Anatomy, Physics and Techniques. Multiple Choice Tutor. By A. Coral and A. T. Irvine, pp 304, 1985 (William Heinemann Medical Books, London), £9 95.
ISBN 0-433-06460-9

This book of multiple choice questions has been produced by two radiologists in training at St Mary's Hospital, London and is designed for those taking the first part of the examination of the Royal College of Radiologists and the higher examination of the College of Radiographers. It is in three parts, the first 122 pages being concerned with anatomy, the second section of 82 pages with physics, and the last 98 pages with radiological techniques and radiography. The right-hand page has two or three five-part multiple choice questions on it, with the answers over the page, often with some explanation and usually a reference to the source of the answer.

It is interesting to see that the authors encounter most of the problems met by all those setting multiple choice questions. These include the use of the word "may"; careless phrasing (does the "lateral wall" of the antrum refer to the antero- or postero-lateral wall?); the answer referring to a different question (14E asks about the right atrium and the answer refers to the left atrium); reference sources that disagree (is the antrum pneumatised at birth?); ensuring that anatomy relates more to radiology than the dissecting room; and avoiding pathology in the techniques section. It is a pity that the authors do not explain clearly in the introduction the rules concerning the numbers of "True" and "False" answers allowed in each question, and that they put radiography in with techniques rather than with anatomy There are a few other inconsistencies present, such as *Radiologic Clinics of North America* appearing in the line of references at the end and not as a journal reference in the text, so that the year of the journal is not given. The proof reading is generally good—I like the idea of the "Crown-Lump" length which appears in 65D.

These criticisms are relatively minor in relation to the mass of referenced information presented, and I applaud the energy of the authors in producing a book that will be eagerly perused by their successors taking the Part I FRCR examination, and those teaching the candidates.

W. D JEANS

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Renal carcinoma: duplex Doppler evaluation

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ABSTRACT

Doppler ultrasound has a clearly defined role in the assessment of carotid and peripheral vascular disease. In these situations vessel pathology produces alterations in velocity and volume flow and in the flow-velocity spectrum. Flow in the renal arteries is affected not only by disease of the renal vessels but also by the peripheral resistance to flow within the kidney. Alterations in this peripheral resistance resulting from renal disease are reflected in the Doppler flow spectrum analysis. In 14 patients with renal carcinoma, three different blood flow patterns were observed, reflecting the differing vascularity of the renal tumours. These were compared with blood flow in normal kidneys and in kidneys containing renal cysts. Doppler ultrasound adds further information to the study of renal carcinomas, allowing the prediction of tumour vascularity, and may be useful as a preliminary investigation prior to angiography and embolisation.

In a modern imaging department, ultrasound occupies a central role in the investigation of a renal mass. It is the logical next step when intravenous urography has demonstrated a renal mass, either incidentally or consequent upon presenting symptoms of a loin mass, haematuria etc. Ultrasound demonstration of a renal cystic lesion has been taken as a clear indication that the lesion is benign and that no further investigation is required (Pollack et al, 1982). Similarly, if there are any atypical features, ultrasound-guided cyst puncture provides direct access to the contents of the cyst, which can be further examined by cytological methods (Elyaderani & Gabriele, 1981). In the evaluation of the solid lesion, however, ultrasound appears to provide less information Although it has been suggested that certain echo patterns are associated with increased vascularity and others with hypovascular lesions, this has not been confirmed (Maklad et al, 1977; Kurtz et al, 1981; Pamilo et al, 1983). Thus ultrasound may be capable of demonstrating areas of necrosis, but this does not provide reliable information concerning tumour vascularity, the demonstration of vascularity has remained the province of angiography.

Doppler ultrasound has found application in the examination of superficial vessels such as the carotid arteries (Atkinson & Woodcock, 1982). Linking pulsed Doppler with real-time B-mode imaging systems allows simultaneous imaging of a vessel and recording of Doppler shift signals from it (Taylor et al, 1978). Duplex Doppler/real-time systems have been used to differentiate dilated bile ducts from vessels (Berland et al, 1982a), cysts from aneurysms, and arteries from veins (Taylor et al, 1978; Goldberg et al, 1982; Dubbins, 1984) More recently attempts have been made to identify a specific role for duplex systems in the assessment of blood flow to the intra-abdominal organs in health and disease (Cole, 1984; Taylor et al, 1985). It is possible, for instance, to detect reversal of portal venous flow in portal hypertension (Tallett & Wilson, 1981), and to evaluate blood flow and predict outcome from a phase of acute rejection in the transplanted kidney (Arima et al, 1979; Arima, 1982; Berland et al, 1982b). Similarly, renal artery stenosis has been demonstrated by Doppler systems in both the transplanted and the native kidney (Greene et al, 1981; Dubbins, 1986). There are, however, no studies to date investigating the effect that disease of the native kidney may have on the nature of the blood flow in the vessel of supply. This study examines the Doppler flow pattern in the main renal artery in patients with renal carcinoma.

MATERIALS AND METHODS

Duplex Doppler B-scan images were examined for 14 patients who presented to the Ultrasound Department, Plymouth General Hospital and who were subsequently diagnosed as having renal cell carcinoma. These scans were compared with those of 14 patients in whom the diagnosis of renal cyst was made from an intravenous urogram and confirmed by ultrasound. While these were not strictly matched controls, the age ranges were similar (42–83 years in the renal tumour group, 52–72 years in the renal cyst group). There were seven men and seven women in the tumour group and eight men and six women in the cyst group; all patients were examined after having fasted for 6 h, in an attempt to reduce bowel gas, using a duplex pulsed-Doppler/real-time system with a 3.5 MHz imaging transducer with 3 MHz Doppler Both kidneys were examined in longitudinal and transverse planes utilising supine, lateral decubitus, and prone positions as necessary The renal arteries were examined in the supine transverse plane and in the left lateral decubitus position, as previously described (Fig. 1) (Isikoff & Hill, 1980; Dubbins, 1986). In addition, however, with the patient in the left decubitus position for the right kidney and the right decubitus position for the left kidney, the

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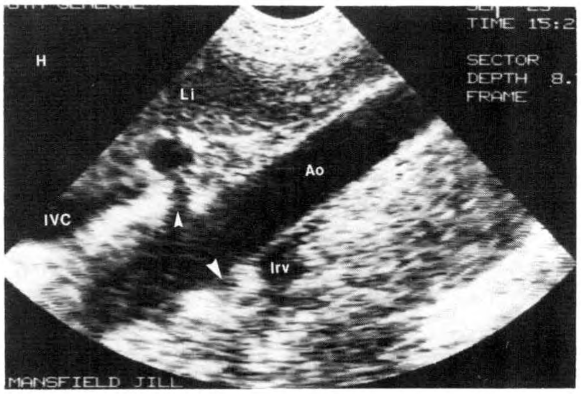

FIG. 1.

Coronal scan of the aorta demonstrating the origin of the right renal artery (small arrowhead) and of the left renal artery (large arrowhead). This position is used in order to identify the origin of the renal vessels and to align the Doppler beam to the proximal renal artery. H = head; Li = liver; Ao = aorta; IVC = inferior vena cava; lrv = left renal vein.

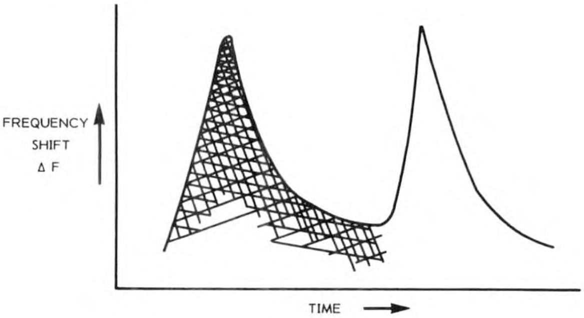

FIG. 2.

Stylised drawing of Doppler frequency spectral analysis showing two cardiac cycles. The cross-hatching in the first cardiac cycle represents the spread of frequencies which occur in the renal vessel. These represent the differing velocities of blood flow occurring instantaneously within the vessels.

Doppler line of sight was placed on the renal artery at the renal hilum and the Doppler flow signal was recorded when possible (Dubbins, 1986). Careful real-time examination of the renal veins and of the inferior vena cava (IVC) was performed, and in seven of the last eight cases of renal tumour a Doppler signal was recorded from the lumen of the IVC and the renal vein (from the affected side). Minimal sample-volume size was used (sample length was 2 mm). The angle of the line of sight of the Doppler beam was adjusted in all cases to achieve the optimum Doppler signal. Hard-copy images of both kidneys and of the renal arteries and veins were obtained where possible. Real-time fast Fourier analysis of the Doppler-shift frequency spectrum is produced by the machine used (ATL Mark 600, Squibb Medical Systems Ltd) (Fig. 2). Images of the frequency spectrum of a representative number of cardiac cycles were also recorded on hard copy or videotape.

RESULTS

The maximum diameter of the renal tumours varied from 5 cm to 16 cm. Their echo pattern varied from echogenic through echo-poor and mixed patterns. In one patient large areas of necrosis were clearly visible. In the patients with renal cysts, the size varied from 3 cm to 8 cm; three patients had more than one cyst (two with two and one with three). The results are summarised in Table I.

Doppler spectral analysis of the patients with renal cysts showed spectral patterns similar to those of a control group in a previous study (Dubbins, 1986). This consisted of a sharp upstroke in systole with a gradual fall to a plateau of constant flow at end-diastole, a pattern likened to a "ski slope". While there was some spectral broadening in diastole this was not unlike results from the control group of the previous study (Fig. 3).

In patients with renal tumours three Doppler patterns emerged. Seven patients demonstrated varying degrees of spectral broadening throughout systole as well as evidence of turbulence, frequently with an associated increase in peak velocity (Fig. 4). The degree of spectral broadening was least in the tumour in Case 9; this tumour appeared to be necrotic at the time of ultrasound examination and at arteriography was demonstrated to be largely hypovascular but with peripheral areas of neovascularity. Three of the remaining seven demonstrated a pattern similar to that seen in the renal cyst group, that is, a normal renal-artery Doppler pattern. Two of these patients were shown by angiography to have a hypovascular tumour. The third had an extremely vascular tumour supplied by an accessory renal artery arising approximately 3 cm below the more usually placed renal artery. Due to technical factors, it proved impossible to achieve Doppler flow recordings from the renal sinus of the affected side in this patient.

In three patients the Doppler flow pattern approximated more to that of a high impedance system. There was a rapid upstroke in systole but with a similarly rapid downstroke in diastole, occasionally with reverse flow in early diastole with little or no forward flow at end-diastole (Fig. 5). In two of these patients echoes could be demonstrated within the renal vein, and attempts to record flow within the vein yielded no evidence of flow. In the third patient the tumour was large and extended across the mid-line, distorting and displacing the inferior vena cava. The renal vein was not identified but was presumed to be occluded by clot or tumour. No renal vein was identified on the late phase of the angiogram in these patients.

TABLE I

PATIENT DETAILS

Case	Size of mass to nearest cm	Grey-scale echo pattern	Doppler flow pattern to affected kidney	Doppler flow in ipsilateral renal vein	Doppler flow to contralateral kidney	Arteriogram
1	7	Mixed echo pattern; fairly even distribution of echo-poor and echo-rich areas	Increased peak frequency with spectral broadening and turbulence	—	Normal	Vascular
2	11	Mixed echo pattern; echo-poor but with scattered echo-rich foci	Increased peak frequency with spectral broadening and turbulence	—	Normal	Vascular
3	6	Mixed, but echo-rich areas predominate	Increased peak frequency with spectral broadening and turbulence	—	Normal	Vascular
4	5	Echo-poor, clot demonstrated in renal vein	High-resistance pattern	—	Normal	Hypovascular Renal vein not demonstrated
5	6	Relatively homogeneous; echo-poor	Increased peak frequency with spectral broadening and turbulence	—	Normal	Vascular
6	4	Echo-poor, very irregular margin with probable perirenal invasion	Increased peak frequency with spectral broadening and turbulence	—	Normal	Vascular
7	6	Mid-range echoes with area of central necrosis	Normal	Detected	Normal	Hypovascular
8	13	Homogeneous echoes slightly greater than adjacent liver. Direct invasion renal vein extension across mid-line	High-resistance pattern	Not detected	Normal	Hypovascular
9	9	Echo-poor but with some echo-free areas suggesting necrosis	Slight increase in peak frequency with turbulence	Detected	Normal	Vascular but with many areas hypovascular
10	16	Entire kidney enlarged with echo-poor areas predominating; invasion of renal vein and IVC	High-resistance pattern	Not detected	Not demonstrated	Hypovascular, renal vein not demonstrated
11	9	Mid-range echoes with areas of calcification	Not demonstrated	Not visualised	Not demonstrated	Predominantly vascular
12	5	Echo-poor with single area suggestive of necrosis	Normal	Detected	Normal	Hypovascular
13	8	Echo-poor	Normal	Detected	Normal	Vascular but supplied by accessory renal artery
14	7	Mid-range echoes	Increased peak frequency with spectral broadening	Detected	Normal	Vascular

One patient was so obese that it proved impossible to obtain Doppler flow signals from the affected side.

Adequate Doppler signals were achieved on the contralateral side in 12 of the 14 patients. In each case these showed the normal Doppler flow pattern.

DISCUSSION

The introduction of duplex Doppler grey-scale imaging devices was an exciting new development in ultrasound, promising that, in addition to the anatomical assessment provided by real-time B-mode imaging, it would be possible to extract physiological information about the nature of blood flow within vessels. While this facility has been used with considerable diagnostic accuracy in the assessment of the carotid vessels in particular, the combination of morphological or structural information with blood-flow data has not achieved widespread use within the abdomen (Atkinson & Woodcock, 1982). Such reports as appeared after its introduction were predominantly anecdotal and described utilisation of the technique to confirm the presence of blood flow to differentiate bile

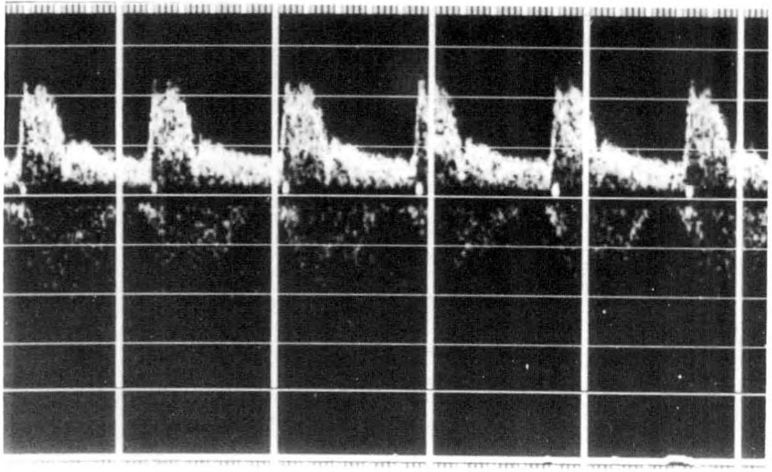

FIG. 3.

Fast Fourier spectral analysis pattern of blood flow within main renal artery to a kidney containing a single 5 cm cyst. This pattern is similar to that seen in renal arteries supplying normal kidneys.

ducts from vessels, aneurysms from other cystic structures and so on (Dubbins, 1984). More recently, it has become possible to assess intra-abdominal vascular disease by Doppler ultrasound. Thus, renal artery stenosis has been demonstrated in both renal transplants and native kidneys by the measurement of velocity and volume flow, and by analysis of the velocity spectrum of blood flow (Greene et al, 1981; Reinitz et al, 1983; Dubbins, 1986).

Hitherto, there have been few reports attempting to assess disease of the end-organ by assessment of changes in blood flow in the vessel of supply. However, early work (Tallett & Wilson, 1981) suggests that it may be possible to evaluate chronic liver disease and portal hypertension by the assessment of flow within the portal vein and to predict renal transplant rejection (Berland et al, 1982a).

It is possible to measure the velocity of blood flow within a vessel based on the Doppler shift frequency, if the angle of incidence of the Doppler beam and the cross-sectional area of the vessel under study are known. Although these quantitative measurements are possible, they depend upon minimising the angle of incidence of the Doppler beam to the vessel, together with accurate measurement of this angle and of the cross-sectional area of the vessel. There are, however, significant difficulties encountered in achieving these measurements. To achieve the optimum angle when investigating vessels within the abdomen is rarely possible. The angle of incidence of the Doppler beam and approach to the vessel are dictated by the patient's body habitus and the presence of bowel gas. Similarly, accurate measurement of the size of the renal artery is difficult. The maximum diameter of the normal renal artery as assessed by ultrasound varies between 5 mm and 7 mm (Dubbins, unpublished), so measurement errors assume great importance in velocity calculations. Thus, while it is possible to assess both the volume and velocity of flow, it is difficult, and results may be subject to a wide margin of error. Bearing in mind these

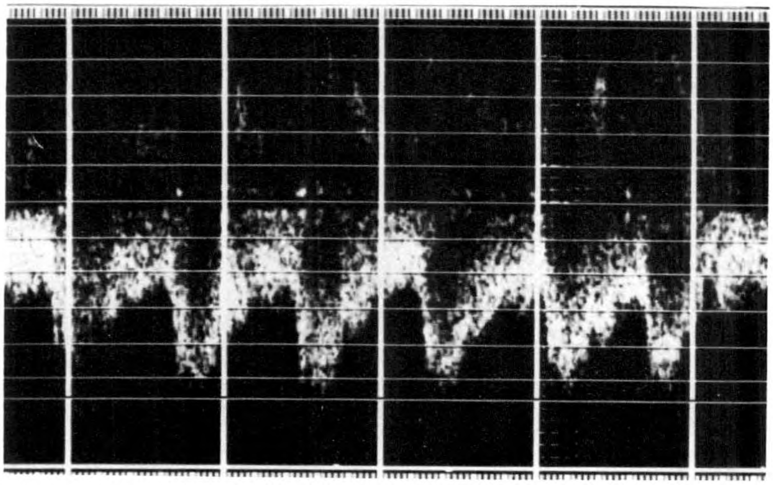

FIG. 4.

Spectral pattern in renal carcinoma. In this figure the blood flow is away from the transducer but the turbulence of flow is demonstrated by the multiple smaller peaks in diastole with spectral broadening and high flow at end-diastole.

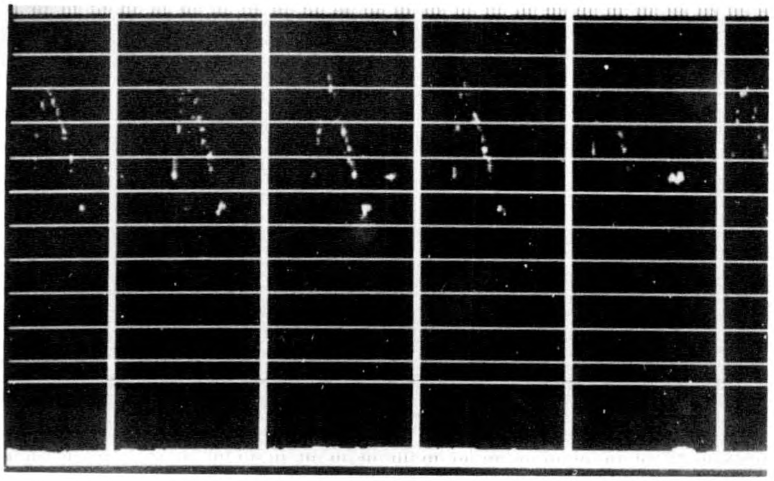

FIG. 5.

Spectral analysis of blood flow in renal tumour with tumour invasion/clot in the renal vein. Blood flow is reversed in early diastole with no flow in late diastole.

difficulties and the time limitations in a busy diagnostic ultrasound department, no attempt was made to quantify blood flow. It is accepted that such measurements are easier with "on-screen" facility for angle measurement together with velocity and volume-flow readout.

The Doppler spectrum of branch vessels of the aorta appears to be specific for each vessel (Cole, 1984; Taylor et al, 1985), but this spectrum depends not only upon the size and shape of the vessel but also on the impedance of the peripheral vasculature supplied by the vessel. The renal artery supplies a low-impedance system which is mirrored in the Doppler spectrum of the normal renal artery, characterised by continuous forward flow during diastole (Figs 2, 3).

Many primary renal carcinomas demonstrate areas of neovascularity with arterio-venous shunting, blood-pooling and early venous filling at arteriography. It was suggested that some of these features might be appreciated on grey-scale ultrasound by differences in tumour echogenicity, although this has not been confirmed by subsequent studies (Maklad et al, 1977; Behan et al, 1980). The only morphological feature that reflects the high blood flow through renal tumours is the increased size of the renal vein (and artery) which may be demonstrated with large, very vascular tumours (Thomas & Bernadino, 1981). If intrarenal arterio-venous shunting is occasionally sufficient to produce detectable morphological change, it seems reasonable to expect that there might be changes in Doppler frequency spectral analysis in patients with vascular renal tumours.

Before the inception of this study, duplex systems were used in an attempt to map areas of neovascularity within renal tumours (Dubbins & Kurtz, unpublished). Though it proved possible to identify areas of abnormal blood flow by placing the Doppler sample volume within the substance of the tumour, this proved to be time-consuming, particularly in patients with largely necrotic tumours.

In this study of the effect of renal tumours on blood flow within the main renal artery, three clear patterns have emerged. In patients with highly vascular renal tumours the vascularity is reflected in the Doppler spectrum by an increase in peak velocity in both systole and diastole, spectral broadening throughout the cardiac cycle, and evidence of turbulence, particularly within diastole. The extent of these changes apparently depends on the vascularity of the tumour. In the second group the angiographically hypovascular tumour demonstrates a normal Doppler pattern indistinguishable from that seen in the normal kidney, or in the kidney containing a simple cyst. The third group, in whom angiography failed to demonstrate a renal vein, were thought to have either renal vein invasion or blood clot within the renal vein. This was suggested on two of the ultrasound examinations by the presence of echogenic material within the renal vein (and by the absence of demonstrable blood flow on Doppler analysis in one), and in the third case by a very extensive tumour growing across the mid-line. In these cases the Doppler spectrum demonstrated an increase in peak Doppler frequency during systole, but a rapid fall in diastole, with reduced flow during the diastolic period, which in one case reached the zero line. These different patterns reflect the vascular supply of the kidney and of the renal tumour. However, the study demonstrates that the technique has significant limitations. The presence of a normal pattern might be expected to indicate a hypovascular tumour, but in one patient the presence of a second renal artery, entirely responsible for blood supply to the tumour, led to the erroneous impression of a hypovascular tumour. At present it is only rarely possible to visualise more than one renal vessel with ultrasound, and in a previous study only one accessory renal artery was demonstrated in a series of 40 patients (Dubbins, 1986).

However, angiography is no longer simply a final method of diagnosis. It is now used in many centres as a pre-surgical procedure in order to decrease vascularity of the tumour by percutaneous arterial embolisation (Wells et al, 1983). It may be possible with the use of duplex Doppler grey-scale imaging to select which patients are most appropriate for this. Thus, those patients in Group 1 would be suitable while those in Groups 2 and 3 are less likely to benefit from pre-operative embolisation. The single case that would be misclassified by this technique could almost certainly be reclassified by assessment of blood flow within the tumour itself

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The mammographic breast pattern and oral contraception

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ABSTRACT

The relationship of oral contraceptive usage to breast parenchymal patterns has been studied in 5319 self-selected women presenting to a breast screening unit. Among pre-menopausal women, 46.1% had taken an oral contraceptive ("the pill") in the past, and 9.5% were still taking the pill. These patients showed a decreased incidence of P_2 patterns and an increased incidence of N_1 patterns. Of the post-menopausal women, 14.7% had been on the pill. Similar differences of incidence of parenchymal patterns are noted in these women. The significance of these changes is unclear.

There are conflicting reports in the literature concerning the relationship between the risk of developing breast cancer and the use of oral contraceptives ("the pill"). Some studies show no relationship or a protective effect (Vessey, 1977; Henneken et al, 1984; Rosenberg et al, 1984), but one report (Pike et al, 1983) has suggested that there is an increased risk of breast cancer in women who have taken highly progestogenic pills for at least 5 years before the age of 25 years. Olsson et al (1985) have recently concluded that women who had started oral contraception at 20 to 24 years of age had three times the risk of developing breast cancer before 46 years of age as non-users.

Wolfe (1976) has reported an association between the parenchymal pattern on mammography and the risk of developing breast cancer.

The present study compares the parenchymal breast patterns, using Wolfe's classification, in women with and without a history of oral contraceptive usage.

PATIENTS AND METHODS

The study was performed on 5319 women who were self-referred to a breast screening unit. All women completed a detailed questionnaire concerning obstetric and gynaecological history and breast symptomatology, with the help of a nurse examiner, followed by a clinical examination by the nurse. Mammography was performed in two planes (lateral and cranio-caudal) for each breast. The radiographs were reported by a single radiologist (G.H.W.) and assigned to a breast-pattern category using Wolfe's criteria.

A history was obtained from the questionnaire concerning the patient's previous and current use of oral contraceptives. The duration of use was noted and, if the patient was no longer on the pill, the time when she had ceased oral contraception. As far as possible, a record was obtained of the type of contraceptive pill. The nurse had samples of many of the more commonly prescribed brands to act as *aides memoire* for patients who were unable to recall the names of their oral contraceptive. The patient was asked if she recognised the pill and its packaging among the presented samples. When more than one oral contraceptive had been used in the past, all the brands were recorded, together with the maximum length of time the patient had been on any one preparation.

The oral contraceptives were then coded according to their type, with emphasis mainly on the oestrogen content. The categories selected were: low-oestrogen (< 35 mg); medium oestrogen (36–50 mg); high-oestrogen ($\geqslant 51$ mg); progestin only, megestrol; chlorimadinone; and "unknown" when a woman was unable to remember the pill she had taken. In practice, the majority of patients received low- or medium-oestrogen pills (Table I). Comparison was made, for the purpose of analysis, between women not taking the pill, women taking a pill containing up to 35 mg oestrogen, and women taking a pill with more than 36 mg oestrogen (combining the high and medium groups). All other pills were excluded because very small numbers of women were involved. Patients who were unable to recall which pill they were on were excluded from the analysis based on type of pill.

All the encoded data were entered into the University of Liverpool IBM 4341 computer and analysed using the SSPS-X statistical package. Statistical analysis was by the χ^2 test.

RESULTS

The results for pre-menopausal and post-menopausal women were considered separately, because the distribution of breast parenchymal pattern is known to

TABLE I

RELATIONSHIP OF BREAST PATTERN TO ORAL CONTRACEPTION IN PRE-MENOPAUSAL WOMEN

	No (%) of women		
Breast pattern	never on oral contraceptive	on oral contraceptive in the past	currently on oral contraceptive
N_1	107 (11.6)	144 (15.1)	33 (16.8)
P_1	64 (6.9)	66 (6.9)	8 (4.1)
P_2	147 (16.0)	114 (11.9)	18 (9.2)
DY	603 (65.5)	632 (66.1)	137 (69.9)
Total	921	956	196

$\chi^2 = 16.9$, d.f. $= 6$, $p = 0.01$.

TABLE II

RELATIONSHIP OF BREAST PATTERN TO TYPE OF ORAL CONTRACEPTIVE CURRENTLY USED IN PRE-MENOPAUSAL WOMEN

Breast pattern	No. (%) of women receiving oral contraceptive	
	≤ 35 mg oestrogen	> 35 mg oestrogen
N_1	17 (12.9)	9 (20.5)
P_1	5 (3.8)	1 (2.3)
P_2	13 (9.8)	3 (6.8)
DY	97 (73.5)	31 (70.5)
Total	132	44

$\chi^2 = 1.95$; d.f. = 3; $p = 0.58$.

TABLE IV

RELATIONSHIP OF BREAST PATTERN TO PREVIOUS ORAL CONTRACEPTIVE IN POST-MENOPAUSAL WOMEN

Breast pattern	No (%) of women	
	never on oral contraceptive	on oral contraceptive in the past
N_1	421 (24.6)	83 (28.0)
P_1	254 (14.8)	42 (14.2)
P_2	392 (22.9)	47 (15.9)
DY	645 (37.7)	124 (41.9)
Total	1712	296

$\chi^2 = 8.13$; d.f. = 3; $p = 0.044$.

change with age and menopausal status (Wolfe, 1976; Whitehouse & Leinster, 1985). Wolfe (1976) has described four types of parenchymal pattern of the breast on mammography: N_1 (normal), P_1 (prominent ducts, limited in extent), P_2 (extensive prominent ducts) and DY (dysplasia). The groups were used in this study.

Pre-menopausal women

In the group of 2073 pre-menopausal women, 921 (44.4%) had never been on the contraceptive pill, while 956 (46.1%) had been on the pill in the past but had stopped taking it within the previous 3 months. A total of 196 (9.5%) were still taking the pill at the time of examination. Marked differences in breast pattern were noted between those who had never been on the pill and those who were on the pill at the time of examination or in the past. The women who had been on the pill had a higher proportion of N_1 pattern and a lower proportion of P_2 pattern (Table I).

A total of 176 women were able to identify which pill they were currently taking, 132 having a low-oestrogen pill and 44 a high-oestrogen pill. Those women on a high-oestrogen pill showed the highest proportion of N_1 and the lowest proportion of P_2 (Table II). The difference did not, however, reach statistical significance.

Of 888 women who could recall which pill they had taken in the past, 393 had received a low-oestrogen pill and 495 a high-oestrogen pill. In these patients, the major differences were noted in women on a low-oestrogen pill. Only 8.1% showed a P_2 pattern, compared to 15.7% in the group not exposed to the pill, with a corresponding rise in the proportion of N_1 and DY (Table III). Again, the differences do not reach statistical significance.

Post-menopausal women

Only 296 (14.7%) of the 2008 post-menopausal women had been on the pill in the past. Those women who had been exposed to the pill showed an overall lower incidence of P_2 and an increase in N_1 and DY compared to women who had not taken oral contraceptives (Table IV). Only 175 women could recall which pill they had taken; 49 had been on a low-oestrogen pill and 126 on a high-oestrogen pill. The figures for breast pattern related to the low-oestrogen pill are probably unreliable because of the smaller number. However, the high-oestrogen pill shows a similar alteration in proportion to that noted in the pre-menopausal women with a rise in N_1 and a fall in P_2 (Table V).

TABLE III

RELATIONSHIP OF BREAST PATTERN BY TYPE OF ORAL CONTRACEPTIVE PREVIOUSLY USED IN PRE-MENOPAUSAL WOMEN

Breast pattern	No. (%) of women receiving oral contraceptive	
	≤ 35 mg oestrogen	> 35 mg oestrogen
N_1	65 (16.5)	71 (14.3)
P_1	24 (6.1)	37 (14.3)
P_2	32 (8.1)	66 (13.3)
DY	272 (69.2)	321 (64.8)
Total	393	495

$\chi^2 = 6.41$; d.f = 3; $p = 0.09$.

TABLE V

RELATIONSHIP OF BREAST PATTERN TO TYPE OF ORAL CONTRACEPTIVE PREVIOUSLY USED IN POST-MENOPAUSAL WOMEN

Breast pattern	No. (%) of women receiving oral contraceptive	
	≤ 35 mg oestrogen	> 35 mg oestrogen
N_1	8 (16.3)	43 (34.7)
P_1	8 (16.3)	17 (13.5)
P_2	10 (20.4)	23 (18.3)
DY	23 (46.9)	43 (34.1)
Total	49	126

$\chi^2 = 7.40$; d.f = 3; $p = 0.06$.

DISCUSSION

Wolfe (1976) has shown a variation in the risk of developing breast cancer between these groups. If N_1 is taken as having a risk of 1, then P_2 has a relative risk of 14 and DY a relative risk of 37.

Wellings and Wolfe (1978) have suggested a firm histological basis for the appearances of breast pattern on mammography. The prominent duct patterns show periductal and perilobular fibrosis with some low-grade atypical lobules, especially in the P_2 type. Dysplastic (DY) breasts have confluent fibrosis and many atypical lobules with severe atypia. Thus "high-risk" mammographic patterns were associated with high-risk pathological features. Moskowitz et al (1980), however, challenge this correlation. A change of breast pattern with age has previously been noted (Whitehouse & Leinster, 1985) and breast pattern is also modified by the patient's weight (Gravelle et al, 1982; Grove et al, 1985), parity and age at first child (Whitehouse et al, 1981).

The effect of the contraceptive pill on breast pattern has been noted previously by Gravelle et al (1980), who found a substantially greater proportion of women with low-risk radiographic patterns (N_1 and P_1) and a lower proportion of women with high-risk patterns (P_2 and DY) in women who had used oral contraceptives.

In both the pre-menopausal and post-menopausal groups of the present study, a history of exposure to the oral contraceptive results in a decrease in the proportion of patients with P_2 patterns and an increase in the proportion with N_1 patterns. The effect is slightly more marked within the pre-menopausal group in those who are still on the pill, compared to those who had taken it in the past. In both pre- and post-menopausal groups there is also a slight rise in the incidence of a DY pattern, compared with those with no history of oral contraception.

It is not known if the radiological appearances of high-risk patterns in the present series are associated with concomitant changes in the histological structure of the breast. Assuming that a radiological–pathological correlation does exist, a shift from P_2 to N_1 would imply a marked reduction in the incidence of histological atypia and a corresponding hypothetical decrease in the risk of breast cancer. Conversely, that group of patients who persist as DY (thus increasing the DY proportion in the contraceptive users) would have an increased risk of breast cancer.

It is noteworthy that the number of women in receipt of a contraceptive pill with an oestrogen content greater than 35 mg was considerably larger in the past than it is now. However, 25% of those currently on the pill are on an oestrogen dose higher than 35 mg.

In pre-menopausal women who had previously been using oral contraception, the lower-oestrogen pill was associated with a marked fall in P_2 and a rise in N_1 and DY, whereas the higher-oestrogen pill was associated with a smaller fall in P_2 and no change in DY. When the pill currently being taken is considered, no significant difference is detected between the different dose levels of oestrogen. This failure to show a difference may be a Type II statistical error resulting from the low numbers involved in this group. For a B value of 0.9 (a 90% chance of showing a difference between the groups), when the expected difference between the groups is of the order of 10%, each group would have to contain 2000 patients.

The meaning of these observed differences is unclear and we are continuing the study in order to relate these phenomena and the history of contraceptive usage to the actual development of breast cancer.

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Book review

Radiology of Liver Circulation, Series in Radiology II. By C. L'Hermine, pp. viii+174, 1985 (Martinus Nijhoff, Amsterdam), £48.50

ISBN 0–89838–715–9

I cannot enthuse on this book, which emanates from the University of Lille, France. It describes the arterial and venographic features in both the normal and abnormal hepatic circulation. There is little that is new in the division of portal hypertension into presinusoidal, sinusoidal, or postsinusoidal aetiologies, and there is much that is controversial or inaccurate in both text and references. For example, it is stated that in intra- or sub-hepatic obstruction, the splenic outflow decreases, the splenic vein is thin, and the spleen cannot enlarge (p. 167). This is one of many incorrect statements; another occurs in the section on Budd-Chiari syndrome, when in a long discussion on the nature of associated splenomegaly (p. 63), the authors refer to a paper written by your reviewer, which in fact made no reference whatsoever to the spleen.

As expected from these publishers, the book is well produced and generously illustrated with high quality arteriograms and venograms. It is a shame that only two subtraction studies are included and that some of the radiographs are dark. Under hepatic venography the authors do not refer to balloon occlusal methods and mention manometry only briefly, the latter being surprising in a work on liver haemodynamics. Angiographic CT is mentioned briefly.

The use of English is idiosyncratic, curious phrases such as "obstacle to flow" and "digestive bleeding" being common. There are numerous misprints (ascutis for ascites, sushepatic for subhepatic) and the book lacks an index.

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Intravenous digital subtraction arteriography: a comparison of peripheral versus central contrast injection

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ABSTRACT

The diagnostic quality of intravenous digital arteriograms using peripheral and central injections in 50 patients were compared No significant difference in diagnostic quality was noted It is concluded that a peripheral injection is the most convenient method of performing an intravenous digital arteriogram.

Intravenous digital subtraction arteriography (DSA) is commonly used for investigating cardiovascular disease (Buonocore et al, 1981; Chilcote et al, 1981; Mistretta et al, 1981, Modic et al, 1982). Two main methods for injection of contrast medium are used· a peripheral injection into an antecubital vein or a central injection into the right atrium. While peripheral injections are quicker and easier to carry out (Popky et al, 1984), better opacification is, theoretically, produced by central injections because the contrast medium is introduced closer to the arterial tree (Hetzel et al, 1954; Rubin et al, 1984)

In this paper we compare the quality of the arteriograms obtained by intravenous peripheral and central injections in a "within-patient" study.

PATIENTS AND METHODS

Fifty patients referred for intravenous DSA were studied (35 men and 15 women). The age range was 28–80 (mean 63) years. Twenty-four of the patients were being followed up after femoro-popliteal by-pass surgery and the remainder for a variety of vascular conditions (Table I). All were subsequently referred (within 3 months) for a repeat examination of the same region. At the first examination the method of injection was randomly selected and on the second occasion the alternative route was employed Two sets of images were, therefore, obtained for each patient, one by the peripheral route and the other by the central route. The diagnostic quality of images was then independently assessed.

A Technicare DR-960 DSA unit was used. The camera has a 10-bit unit with a 1.2 mm × 1.2 mm focal spot. Images were obtained at the rate of 1 frame/s on a 512 × 512 matrix using a 12 in field. Following data acquisition, the best possible image was obtained via the mask and cine-frame combination. Hard copies were made using a standard multiformat camera.

All injections were performed using a Medrad intravenous injector. For the peripheral route a 16-gauge 51 mm cannula was inserted into an antecubital vein. For the right atrium injections, a 5 French, 65 cm straight catheter with side-holes and an end-hole was introduced over a guide-wire inserted through an antecubital or a femoral vein. A total of 50 ml of the non-ionic contrast medium iopamidol 370 was injected at 15 ml/s with a 0 1 s delay for each projection, at each site. In addition, for the peripheral injections, 25 ml of physiological saline was layered on top of the contrast medium within the syringe in order to flush the contrast medium from the arm.

RESULTS

Thirty-eight (76%) of the 50 pairs of images obtained were considered by the independent observer to be of equal diagnostic quality (Fig. 1). Six (12%) of the images obtained by the peripheral route were considered to be of less diagnostic value, and this was attributed in three of these to movement artefact, in two to bowel gas overlap and in one to a generalised increase in image noise (Fig. 2). An equal number (12%) of images obtained by the central route were considered to be of less diagnostic value (Fig. 3). In one of these this was attributed to excessive background noise and in another to bowel-gas overlap.

Overall, excluding artefacts, four (8%) of the peripherally obtained images and one (2%) of the centrally obtained images were considered to be of more diagnostic value than their corresponding counterparts.

DISCUSSION

The non-ionic contrast medium iopamidol 370 was used for all the examinations because it has been shown to be better tolerated for venous injection (Grainger, 1980). Because of the fast injection, the only symptom of which the patients complained was a feeling of heat and, if warned in advance, they found this acceptable. Because of the absence of nausea and vomiting, movement and swallowing artefacts did not occur.

A number of animal experiments have shown conclusively that the best arterial opacification, other than by arterial injection itself, is produced when

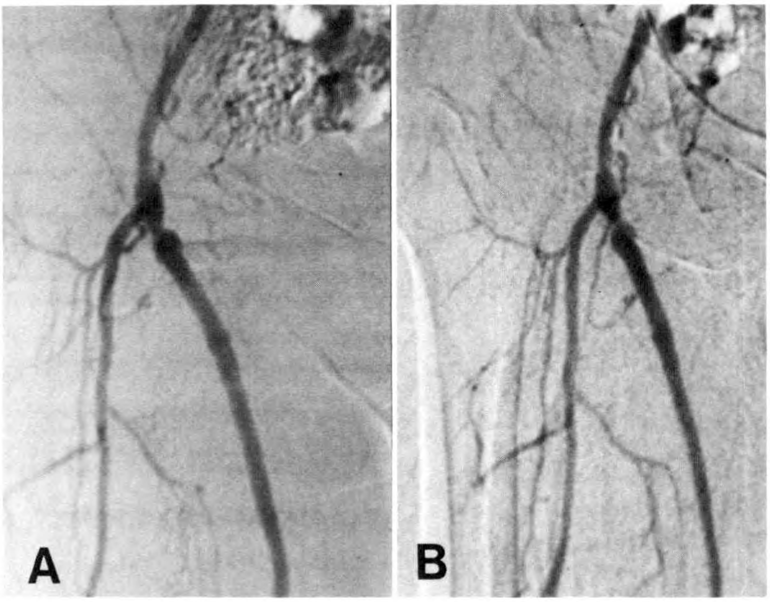

Fig. 1.

(a) Peripheral injection. (b) Central injection. The images are of the same diagnostic quality.

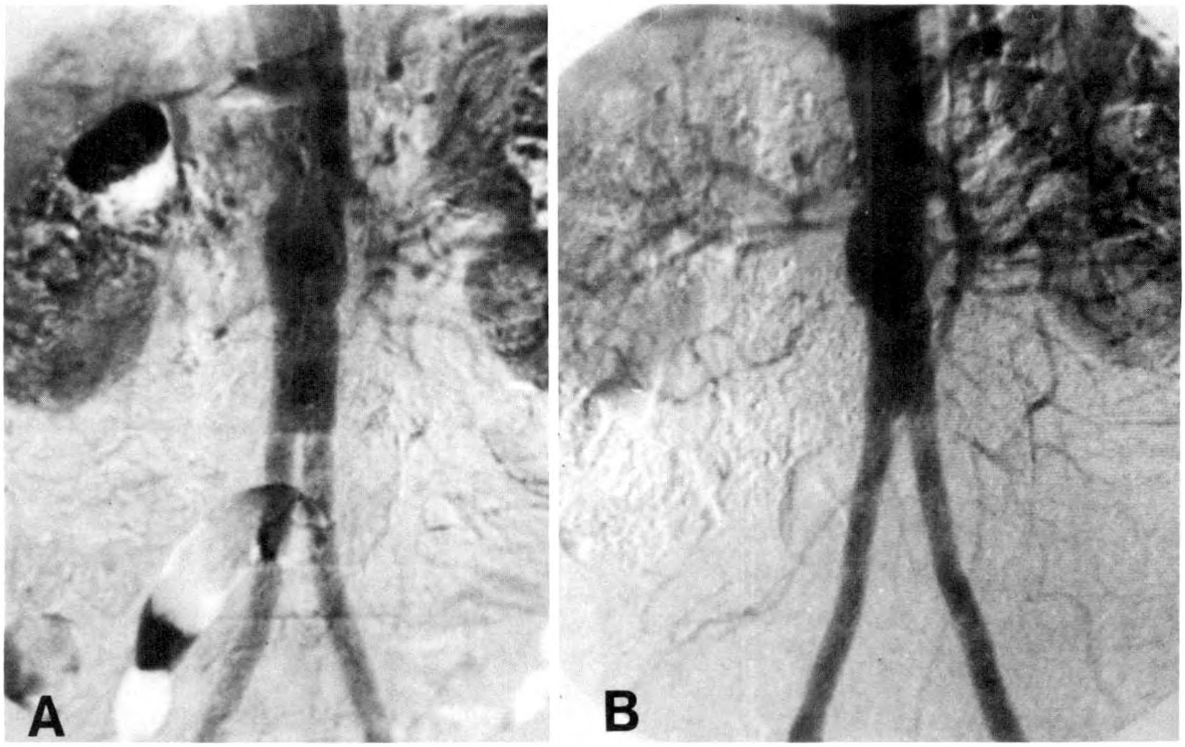

Fig. 2.

(a) Peripheral injection. (b) Central injection. The renal and visceral arteries above the aneurysm are not as well seen in (a) due to overlying bowel artefacts. The right limb of the graft is also less well seen for the same reason. However, the patency of the aortic graft (the clinical problem) has been established by both injection techniques.

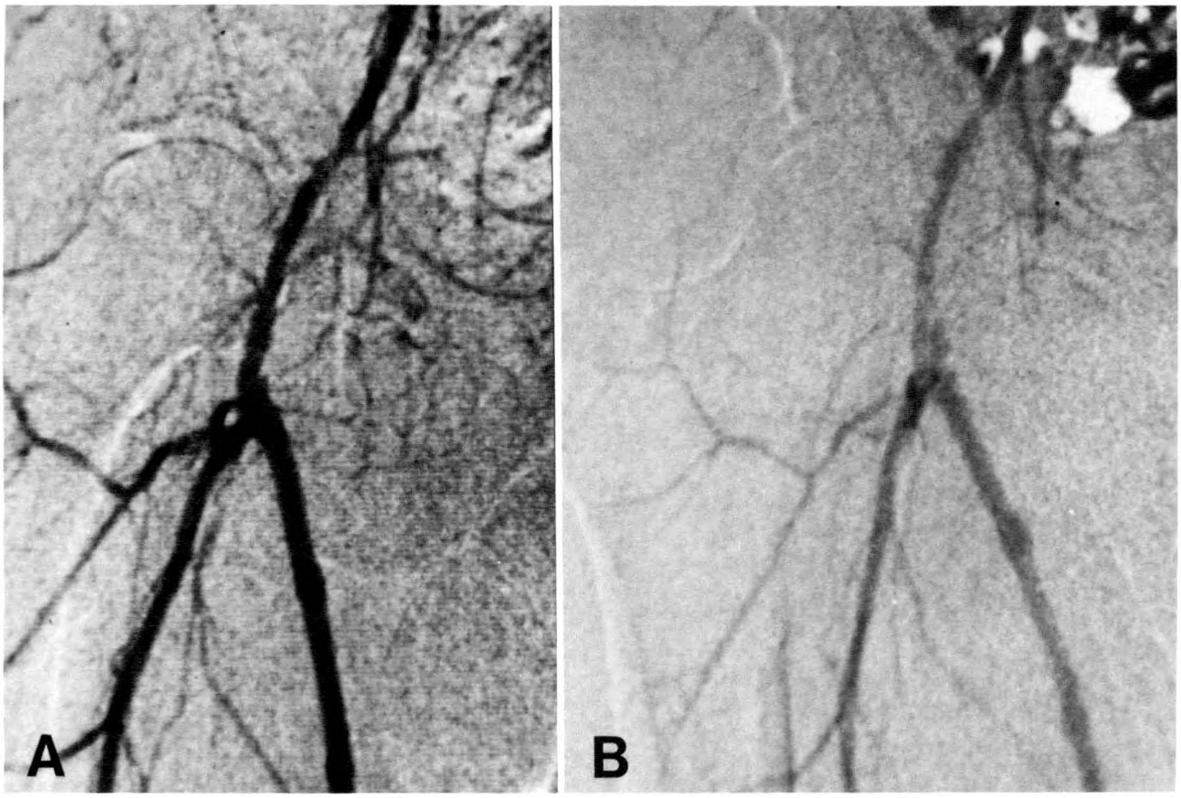

FIG. 3.

(A) Peripheral injection. (B) Central injection. The diagnostic quality of the two images is satisfactory but in this instance the central injection image (B) is slightly less clear.

intravenous contrast medium is injected into a pulmonary artery (Rubin et al, 1984). However, in practice, catheters passed through the right ventricle into the pulmonary artery tend to produce arrhythmias, and so this route has not been advocated, most investigators preferring to inject into the right atrium. When investigating patients, as distinct from animals, a number of factors influence the density of arterial opacification, such as the central blood volume, the quantity of contrast medium injected, the osmolality of the contrast medium and the injection rate (Burbank, 1984). However, the most important factor is the cardiac output, which is often reduced in patients, like those in this series, who have generalised arteriosclerosis with associated myocardial ischaemia. In this study, however, many of these patient-related factors were eliminated because the peripheral and central injection examinations were carried out in the same patient within a few weeks of each other.

It is probably because of the variable physiological factors that in this series no significant difference in the diagnostic quality of the intravenous arteriograms could be detected, irrespective of the injection route. Certainly, peripheral injections are easier and quicker to perform, a fact appreciated by many patients in this series because multiple follow-up examinations are often required. Although the main expense involved in intravenous DSA using non-ionic contrast media is the cost of the contrast medium itself, intravenous cannulas are considerably cheaper than central line catheters, a factor which needs to be considered when large numbers of examinations are being carried out. Furthermore, central venous catheterisation is not always straightforward. While catheterisation from the basilic vein to the right atrium is usually easy, if the cephalic vein has to be used, the passage of the catheter is often obstructed by the clavi-pectoral fascia preventing the catheter entering the superior vena cava. Nor is central venous catheterisation without risk: the veins may be damaged, leading to later thrombosis, and thin-walled structures such as the superior vena cava or right atrium may be punctured by the guide-wire or catheter, or by the injection itself. This may result in mediastinal extravasation (Rosen et al, 1983; Pinto et al, 1984; Gibson et al, 1985), although rupture by the injection is less likely if a pigtail catheter, rather than a straight one, is used (Rosen et al, 1983). Patients in whom central catheterisation was not possible were excluded from this series as results could not have been compared. No serious complications of central injections were encountered.

Rupture of peripheral veins of the arms does occur on rare occasions (Modic et al, 1983), but this can be minimised if the injection rate is not too high, for example 15 ml/s, as used in our patients. During injection the arm can be carefully observed and, if there is evidence of venous rupture, the injection is stopped. When non-ionic contrast medium is used, extravasation is not painful, as it is with conventional media, probably because non-ionic media have a similar osmolality to that of tissue fluids (Lea Thomas & Briggs, 1984). In only one of the patients in this series did rupture occur, requiring replacement of the catheter.

For peripheral injections we consider that layering of the contrast medium beneath normal saline is important to flush the contrast medium from the arm veins.

Previous studies have been carried out on patients comparing the diagnostic quality of intravenous arteriograms using peripheral and central injections but with conflicting conclusions. Whilst Saddekni et al (1984) and Modic et al (1983) conclude that a consistently higher quality was obtained with central injections, Popky et al (1984) generally found that there was no significant difference in overall image quality attributable to the injection site. Our experience supports the latter view.

We therefore conclude from this "within-patient" comparative study that, as there is no significant difference in image quality, for the convenience of patients, peripheral injections are the most acceptable way of performing digital arteriograms.

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A detailed study of radiation dose and radiographic technique during chest radiography

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ABSTRACT

The radiation dose to a series of patients referred for chest radiography has been monitored using thermoluminescent dosimetry. The postero-anterior projection was employed throughout the study. Measurements were made in two rooms of the same general hospital. Each room was equipped with automatic exposure control of the air ionisation chamber type. The effect of this equipment on patient exposure was investigated and compared with manual exposure control. In all cases the tube potential (kVp) was selected by the radiographer but tube current (mA) was determined by the generator. Anterior and posterior radiation doses were measured using sachets of lithium fluoride. For each group of patients the anterior exit dose, and therefore all of the radiation dose, was lower when automatic control was used. The standard deviation on the anterior patient dose was lower under automatic control, which resulted in fewer films needing to be repeated due to incorrect film density. Film densities were also investigated using a densitometer, to provide a further comparison between the two types of exposure control

The chest radiograph is the most commonly requested radiological procedure (31.6%) (Kendall et al, 1980). Nevertheless, even the most experienced radiographer can, on occasion, find it difficult to choose the correct exposure factors for optimum diagnostic film quality. Automatic exposure devices aim to produce correctly exposed radiographs irrespective of the thickness and composition of the subject, and fewer films should need to be repeated due to incorrect density of the radiograph. This is achieved by adjustment of the mAs value, while the kVp can be selected by the operator for adequate penetration and contrast.

Automatic exposure control devices are common additions to modern generators. Two principal types of detector are used to achieve control of film density: the air ionisation chamber and the fluorescent screen. In the former, the charge produced by the passage of X rays is collected by a capacitor; the second method relies on luminescence produced by the action of X rays on a fluorescent screen being detected and amplified by a photomultiplier tube to produce a charge in a capacitor. In both devices, when the capacitor is charged to the desired value, the exposure is terminated.

The aim of this survey was to investigate two aspects of the operation of automatic exposure control devices in radiography. Firstly, these devices should terminate the radiographic exposure at a given constant entrance dose to the film. This should, therefore, result in fewer radiographs needing to be repeated because of incorrect exposure. Secondly, this reduction in the number of repeat radiographs should reduce the radiation dose to the patient. Chest radiography was chosen because the positioning of the patient is particularly difficult whilst using automatic exposure control, and therefore places extra demands on the radiographer.

MATERIALS AND METHOD

The radiation doses to a series of patients referred for chest radiographs were assessed in two rooms (A and B) fitted with automatic exposure control devices of the air ionisation type. Entrance and exit doses were measured using lithium fluoride thermoluminescent dosemeters (TLDs). An experimentally determined energy response calibration factor was applied to these X rays, while the background signal for each group of dosemeters was measured and subtracted from the readings of the separate patient dosemeters.

The initial set of exposure factors had been determined by the usual practice of accepting a satisfactory film and using these factors as a baseline. For an average 70 kg man these were: 60 kVp and 16 mAs using and FFD of 2 m with Du Pont Quanta II intensifying screens and Cronex 7 film processed through a daylight handling system.

Variations in patient weight, size and composition necessitate modifications in radiographic technique. This is at the radiographer's discretion and is based on experience. A postero-anterior (PA) projection is always used, centred on the mid-line at the level of the fourth thoracic vertebra. The tube is then angled caudally and collimated to reduce the area irradiated to a minimum. Thicknesses of all chests were measured, using calipers, at the level of the sternal angle with the arms raised.

Initially, patients in the survey had TLDs positioned:

(i) posteriorly 5 cm medially to the angle of scapula;

(ii) anteriorly at a point in the mid-clavicular line 10 cm caudally to the inferior edge of clavicle.

Later patients had the anterior (exit dose) TLD positioned at the sternal notch.

In chest radiography, the choice of the dominant ionisation chamber and its position relative to detailed anatomy is critical. Based on experience, the right lower ionisation chamber of the automatic exposure control was chosen as the dominant field so as to avoid, as far as possible, the heart shadow. A density increase of 2 on the fine control was necessary to produce an optimum density range for both generators. Under automatic control neither machine provided a readout of mAs, and as both were multipower register generators, mA was not determinable either. Actual mAs was therefore obtained by direct connection of a suitable meter.

Details of the examination and patient data were recorded on a standardised form. The number of radiographs taken and, where necessary, the reasons for any repeat exposures, were noted.

Initially, comparisons of radiographs of different patients, resulting from manual and automatically controlled exposures, were made visually. However, to ensure that lower-contrast radiographs were not being accepted by the radiographers, optical density measurements were made using a densitometer. In order to obtain information on image contrast, density readings were made at the second thoracic vertebra and at an area within the lung apex. These areas were chosen to provide a reasonable representation of average film densities, for contrast assessment. Maximum density and base plus fog levels were also measured.

In addition, when the mAs product was known, the posterior dose was also calculated using the method of Harrison et al (1983). This method requires a knowledge of the technique factors and tube output data. Allowance must be made for backscatter if the tube output is measured in air. It is impossible, however, to calculate the anterior dose accurately without a detailed knowledge of the composition of the patient's tissues.

Analysis of variance was employed to compare the means from the sets of patient radiographs for the two rooms and for manual/automatic control. A difference between the means was considered to be statistically significant at the 95% confidence level ($p < 0.05$). Where it was considered appropriate, further tests using analysis of covariance were performed to investigate the effect of both tube potential and chest size on radiation doses; a linear adjustment was made to the data to compensate for any differences in these parameters; trend in the data was taken to be significant at the 95% confidence level. Linear regression was used to investigate further the effect of both tube potential and chest size on patient doses. Scheffé's method (Scheffé, 1959) was employed to compare anterior doses under automatic control in Room B, and the same level of statistical significance as above was applied.

Results

A summary of the average technique factors and patient information for each group of patients is shown in Table I, the standard deviation on the mean value being given. As may be seen from Table I, all examinations were performed at a tube potential of about 60 kVp. The ranges of ages and chest thicknesses were not great either.

Patients were monitored in four separate groups. The first group comprised those monitored at the mid-clavicular line under both automatic and manual control in Room A (*i.e.* the first two columns in Tables I, II and III). Data on the second group are shown in the third, fourth and fifth columns of Tables I, II and III, while patients examined in Room B at a constant 60 kVp and 70 kVp formed the third and fourth groups, respectively. All patients in a single column will be referred to as a set.

Table II is a summary of the mean radiation doses received by each group of patients, together with information on the mean measured film densities. For the patient examinations where the mAs product was known, it was possible to calculate the posterior dose using a method described by Harrison et al (1983), and the results of these calculations are also given in Table II.

The radiation-dose data presented in Table II may be employed to estimate the dose to other organs using normalised dose data (Gray et al, 1981). It is necessary to multiply the normalised dose data by the entrance doses, which for a PA projection will be given by the posterior dose value.

Discussion

It is apparent from inspection of Table II that there is a large spread in the mean radiation dose at both anatomical positions for each group of patients in the

TABLE I

Average technique factors and patient information (± standard deviations)

	Room A			Room B			
	*Manual	*Automatic	Automatic	Manual	Automatic	†Automatic	†Automatic
No. of patients	21	20	10	11	10	20	20
Tube potential (kVp)	56±4	60±4	62±4	60±3	59±4	60	70
Age (years)	41±17	51±13	42±13	43±18	48±21	35±15	43±15
Chest thickness (cm)	21±2	22.5±2.5	21.5±4	21.5±3	23±3	20.5±2	21.5±2

*Exit dose measured on mid-clavicular line.

†Tube potential fixed.

TABLE II

MEAN RADIATION DOSES AND FILM DENSITIES (± STANDARD DEVIATIONS)

	Room A			Room B			
	*Manual	*Automatic	Automatic	Manual	Automatic	†Automatic	‡Automatic
Anterior dose (mGy)	0.07±0.03	0.03±0.02	0.04±0.02	0.06±0.03	0.05±0.02	0.02±0.02	0.02±0.02
range	0.00 – 0.17	0.01 – 0.09	0.00 – 0.07	0.01 – 0.12	0.00 – 0.10	0.00 – 0.05	0.00 – 0.10
Posterior dose (mGy)	0.50±0.18	0.38±0.15	0.39±0.17	0.31±0.11	0.41±0.11	0.36±0.12	0.25±0.02
range	0.33 – 1.11	0.21 – 0.70	0.15 – 0.66	0.22 – 0.60	0.27 – 0.61	0.23 – 0.60	0.16 – 0.42
Calculated posterior dose (mGy)	0.37	0.28	—	0.28	—	—	—
Density							
Base/fog	0.23±0.01	0.23±0.01	0.22±0.01	0.25±0.02	0.25±0.01	0.20±0.01	0.22±0.01
Maximum	3.04±0.12	3.14±0.28	3.37±0.16	3.23±0.10	3.22±0.18	3.58±0.10	3.30±0.21
Second thoracic vertebra	0.54±0.10	0.52±0.13	0.58±0.09	0.52±0.04	0.61±0.17	0.62±0.10	0.71±0.10
Apex of lung	1.24±0.25	1.07±0.16	1.40±0.09	1.20±0.18	1.55±0.09	1.78±0.29	1.64±0.19

*Exit dose measured on a mid-clavicular line.
†Tube potential fixed (60 kV).
‡Tube potential fixed (70 kV).

two rooms. One would not expect any variation in anterior dose for patients radiographed under automatic exposure control; however, some variation is seen. The spread arises for two main reasons:

(i) differences in the position of the chambers relative to detailed anatomy;
(ii) background signal variations on the TLD reading.

On average, the standard deviation in the anterior dose results is lower under automatic exposure control. This would be expected to be reflected in a lower incidence of exposures repeated due to incorrect technique factors and, in practice, this was found to be the case, as the reject rates, due to incorrect film density under automatic and manual control, were 1.3% and 6.3%, respectively.

No difference ($p = 0.20$) in the mean anterior doses under automatic control was noted for the two sets of patients in Room A monitored at the mid-clavicular line 10 cm caudally to the inferior edge of the clavicle and the sternal notch. Thus the position of the anterior dosemeter had no effect on the measured dose. Linear regression was performed on the data and there was no evidence ($p = 0.16$) that anterior doses under automatic control in Room A were dependent on either chest thickness or tube potential. Thus, the automatic exposure device in Room A adequately compensates for changes in both patient size and tube potential.

A similar analysis was performed on the posterior doses for the two sets of patients in Room A, radiographed under automatic control, and no significant difference ($p = 0.87$) in the means was noted. Linear regression analysis indicated that there was a statistically significant dependence of radiation dose on chest size ($p = 0.001$, slope $= 39\,\mu$Gy/cm) as might be

TABLE III

CALCULATED ORGAN DOSES (mGy)

	Organ	Room A			Room B			
		Manual	Automatic	Automatic	Manual	Automatic	†Automatic	‡Automatic
Measured data	Thyroid	0.14	0.11	0.11	0.09	0.11	0.10	0.07
	Active bone marrow	0.07	0.05	0.05	0.04	0.06	0.05	0.03
Calculated data	Thyroid	0.06	0.04	0.04	0.04	0.05	0.04	0.03
	Active bone marrow	0.09	0.07	0.07	0.06	0.08	0.07	0.05

†Tube potential fixed (60 kVp).
‡Tube potential fixed (70 kVp).

anticipated. However, tube potential did not have a statistically significant effect on posterior dose. When posterior doses were compared for the two sets of patients examined under automatic control in Room A (with a linear adjustment for changes in chest size and tube potential) no difference in the means was observed.

An overall comparison was made between the automatic and manual doses in Rooms A and B. Mean anterior manual doses from Rooms A and B together were compared with the mean automatic dose from both rooms. The mean anterior dose under automatic control was 0.03 mGy, which is significantly less ($p < 0.001$) than the mean manual dose (0.06 mGy) Further analysis indicated that the manual exposures were consistent in both rooms, as were the automatic exposures.

Posterior doses under manual and automatic exposure control were compared in Rooms A and B. Posterior doses, adjusted for changes in both tube potential and chest thickness, were greater under manual control in Room A ($p < 0.0001$). However, in Room B no significant difference was noted between manual and automatic doses.

Anterior doses under automatic control in Room B were compared. This analysis indicated that there was a statistically significant difference ($p = 0.002$) between the mean dose to the set of patients who were radiographed at varying tube potential (Table II, Column 5) and that to those patients radiographed at a constant tube potential. No difference was noted between the mean anterior doses for the two sets of patients examined at constant tube potentials It was deduced from the results of the linear regression analysis that the automatic exposure control adequately compensated for any changes in either tube potential or patient thickness. The high mean anterior dose for those patients radiographed with varying tube potential may be due to the method of background signal subtraction (see later).

Differences between the mean posterior doses for the three sets of patients examined under automatic exposure control in Room B were statistically significant ($p = 0.0001$). There was a significant dependence of posterior dose on chest size ($p < 0.0001$, slope $= 30.7\,\mu$Gy/cm). Posterior doses also varied with tube potential but this was not quite statistically significant ($p = 0.09$, slope $= -15.4\,\mu$Gy/kV). When a linear adjustment for changes in both tube potential and patient thickness was made to the posterior dosemeter readings, no difference was noted between the three sets. Thus, the differences between the mean posterior doses for these three sets is due to changes in both patient size and tube potential.

Linear regression analysis was performed on all the posterior doses, including both manual and automatic exposure control. It was deduced from these results that a larger chest size was associated with a greater posterior dose ($p<0.0001$, slope$=33\,\mu$Gy/cm), whilst increasing the tube potential decreased the posterior dose ($p = 0.01$, slope $= -6.9\,\mu$Gy/kV), as might be anticipated.

Film density was measured at four positions on the radiographs to investigate whether there was a decrease in density with automatic exposure control. A summary of these results is given in Table II, inspection of which indicates that film densities at the two anatomical positions were higher under automatic exposure control. The variations in film density at the second thoracic vertebra and the apex of the lung are somewhat lower than the variations in dose, due to the logarithmic relationship between density and dose. In general, the film density variations are lower at the second thoracic vertebra and higher at the apex of the lung under manual control. With automatic exposure control selected, the film density at the two anatomical positions should be constant. Differences in the position of the chambers relative to detailed anatomy and changes in patient size, composition and processing conditions have caused the variations in film density under automatic exposure control.

Measured and calculated posterior dose values may be compared (see Table II). The calculated values are on average 0.09 mGy lower, but are within one standard deviation of the mean measured value.

The thyroid dose estimation using measured, normalised organ dose data varied between 0.06 mGy and 0.12 mGy, and that using the calculated dose data was approximately 50% lower (see Table III). The estimated mean dose to the active bone marrow varied between 0.04 mGy and 0.08 mGy, using the calculated normalised organ-dose data with the corresponding figures for the measured data being, on average, 30% lower (see Table III). Radiation doses to the testes, ovaries and uterus will be considerably lower than the active bone marrow dose (by a factor of between 25 and 160). This arises because the normalised organ-dose data values are correspondingly lower. The estimated gonadal doses are in reasonable agreement with previously published results (Wall et al, 1980).

The uncertainty in the measured dose values mainly arises from the method of subtracting the background signal from the dosemeter readings. In particular, it is dependent on the fluctuation of the background signal. The percentage error which this introduces will vary with the magnitude of the radiation dose, and for the anterior dose with lithium fluoride dosemeters could be as high as 100% and may be a limiting factor in comparing different sets of patients. Posterior dose readings will have a maximum anticipated measurement error of approximately ±10%. As the observed standard deviation is considerably greater than this, differences between individual patients must be the main reason for these fluctuations. The posterior doses, calculated from the technique factors, will have an anticipated error of ±8% (Harrison et al, 1983). Patient variability will lead to large uncertainties in the estimated organ dose values. It is difficult to quantify the cause of fluctuations in the film density measurements, but these will arise from differences in processing conditions, patient composition and size, and the position of the chambers relative to detailed anatomical features.

CONCLUSIONS

The standard deviation of the anterior dose was lowest under automatic exposure control, which in turn resulted in fewer exposures needing to be repeated due to unacceptable film density. It was deduced from the results of linear regression analysis of the anterior doses that differences in both tube potential and chest thickness were compensated for by the automatic exposure control devices.

Mean anterior doses were lowest under automatic control, and this result was statistically significant at the 99.9% confidence level. Since the anterior dose is lower, all radiation doses will be lower. These findings indicate that in this hospital, at least, the use of the air ionisation chamber type of automatic exposure control has resulted in lower patient doses.

Posterior doses were also compared, and the use of automatic exposure control resulted in significantly lower doses in Room A. However, in Room B there was no significant difference between manual and automatic posterior doses.

Linear regression analysis of all the posterior doses indicated that thicker patients received higher doses, and increasing the tube potential reduced posterior doses. On the other hand, the use of a higher tube potential decreases the image contrast on the developed film. However, it was decided that the lower patient doses justified the acceptance of a partially reduced range of image contrast, and this slightly higher kVp technique has now been adopted as the standard procedure in this hospital.

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Book reviews

Iatrogenic Disorders of the Fetus, Infant, and Child. By G. Kassner, pp. xxiv + 375, 1985 (Springer-Verlag, Heidelberg), DM440

ISBN 0–387–90930–3

Most of us who read the annual reports of the Medical Protection Societies have that uneasy feeling that "there but for the grace of God go I". If these publications are alarming, this one is positively frightening. It is however a comprehensive treatise on what can go wrong with children at the hands of their medical attendants. This volume considers complications of simpler and more invasive radiological procedures, complications of cardiac catheterisation and angiography, and of neurodiagnostic studies, iatrogenic disorders of the fetus, birth trauma, perinatal asphyxia, and iatrogenic respiratory distress, as well as generally considering complications of neonatal intensive care. Further topics include complications of drugs, nutritional therapy and immunisation, and the complications of treatment of childhood cancer.

Virtually everything that could conceivably go wrong is recorded and illustrated, and the bibliography is very extensive. I could, however, find no reference to AIDS, but no doubt this will feature in future editions of this book, which presumably will be larger, reflecting the continuing damage done to our patients—the cost of more sophistication in medical treatment. The companion volume of this book will deal with the complications of surgery.

D. G. Shaw

Galliumszintigraphie. By H Botsch, pp. 90, 1985 (Springer-Verlag, Berlin), DM58

ISBN 3–540–13809–9

This is a concise publication which aims at reviewing the clinical indications for gallium-67 soft tissue total body scintigraphy. Out of a total of 90 pages, approximately 60 are dedicated to a review of clinical applications in a variety of clinical entities. The book is well produced. The 40 or so plates are of good quality, and many of them compare the gallium studies to conventional radiology and/or X-ray transmission tomography when indicated. The text is well cross-referenced and over 300 references are listed. From these, less than 10 are from 1984 onwards. Since the book is dedicated to gallium scintigraphy only, it fulfills its aim to be a concise, easily readable review of the clinical applications of this radionuclide. Since it is entirely written in German, it will only be of interest to those who have some knowledge of this language. As expected, this small monograph does not review recent developments with indium-111 labelled white cells, and the more recent interest in technetium-99m labelled porphyrins. In nuclear medicine, as in any areas of medicine, time passes rapidly.

P. J. Ell

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Radiation therapy of squamous carcinoma of the tonsil: an analysis of prognostic factors and of treatment failures

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ABSTRACT

A retrospective analysis of the results of treatment by primary irradiation of 87 cases of squamous-cell carcinoma of the tonsil at one institution over a 20-year period is presented. Survival at 5 years for all patients was 20%. The major determinants of survival were tumour size (T) and nodal status (N) at presentation. Degree of histological differentiation had no prognostic significance. Initial failure occurred in the primary tonsil site or in cervical lymph nodes in almost all cases. It is clear that treatments that increase loco-regional control are needed if the prognosis for the more advanced tumours is to be improved and it is suggested that a combined-modality approach (surgery plus irradiation) needs to be explored. For early lesions, primary radiation therapy remains the treatment of choice.

In the United Kingdom, the incidence of carcinoma of the tonsil is eight cases per million population and in otolaryngological practice it is the second most commonly seen malignant tumour (Stell, 1976). Patients commonly present at a late stage when the tumour is extensive and with cervical nodal metastasis (Stell, 1976). This late presentation of patients is reflected in the current treatment reports which have not shown any significant improvement in patient survival, despite improvements in techniques in recent years (Coutard, 1932; Lederman, 1967; Doyle et al, 1978).

The standard method of treatment in the past has been external irradiation for all squamous-cell tonsil carcinomas, the aim being curative for small tumours and palliative in large tumours. Controversy exists as to the current role of surgery. It has been recommended that combination surgery and radiotherapy should be employed for small tumours with cervical metastasis and for larger tumours with or without cervical nodal involvement. The place of chemotherapy has yet to be determined (Stell, 1976).

This retrospective study is a review of the results of primary curative radiation therapy for squamous-cell carcinoma of the tonsil as employed over a 20-year period (1962–81), in Nottingham. The purpose of this study was to analyse the factors that affected patient survival, to identify the patterns of treatment failures and to identify factors which may improve patient survival by better use of all current treatment modalities.

PATIENTS AND METHODS

The case records of all patients with histologically proven squamous-cell carcinoma of the tonsil seen in the Department of Radiotherapy at Nottingham General Hospital from 1962 to 1981 were reviewed. The 87 patients so identified are included in this study. They were a consecutively treated group. In this series the median age was 64 years and the age range 42–91 years. The male-to-female ratio was 2 : 1. During the 20-year study period, standard curative therapy for squamous-cell carcinoma of the tonsil in Nottingham was by external irradiation. This was delivered by a ^{60}Co unit or a 6 MV linear accelerator in the great majority of cases. The technique, dose and fractionation were by no means uniform, but in most cases the patients were treated in a shell, using two wedged fields to include only the primary tumour and any clinically significant lymphadenopathy. It was not the policy over this period to attempt elective irradiation of any clinically uninvolved nodal areas. The usual "radical" regimen consisted of either 60 Gy over 5 weeks or 52.5 Gy over 3 weeks

No patients received planned combination therapy, but a small number of patients with recurrent or persistent disease were treated by surgery, chemotherapy or further irradiation.

The patients were classified according to the International Union Against Cancer (UICC) TNM system (UICC, 1978) (Table I). No patient had evidence of distant metastases prior to commencement of treatment. The histological diagnosis was reviewed by one of the authors, (J.C.) according to the World Health Organization (WHO) classification (Wahi,

TABLE I

TNM CLASSIFICATION (ALL PATIENTS)

	N_0	N_1	N_2	N_3	Total
T_1	10	4	1	1	16
T_2	13	9	3	15	40
T_3	6	8	0	10	24
T_4	0	1	0	6	7
Total	29	22	4	32	87

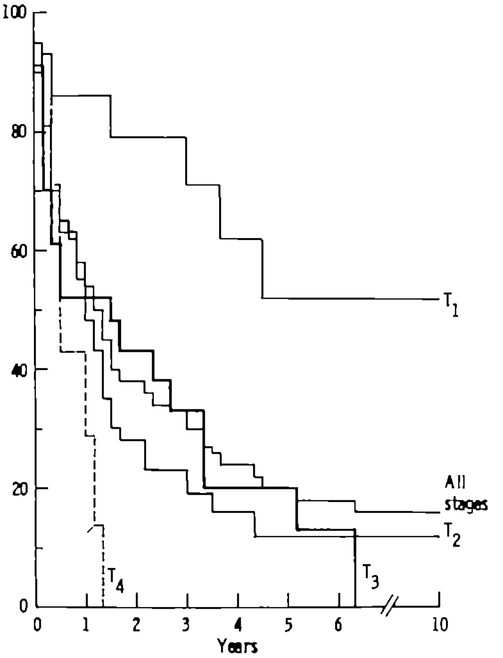

FIG. 1.

Survival by T stage, including deaths by intercurrent disease.

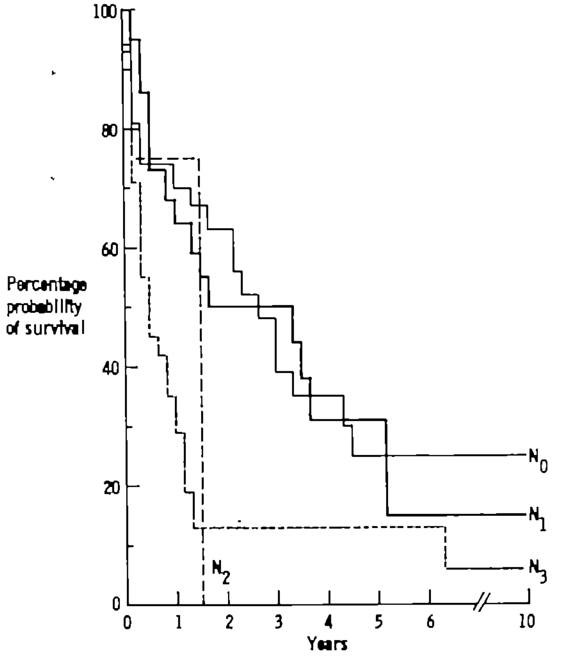

FIG. 2

Survival by N stage, including deaths by intercurrent disease

1971), in the 54 of the 87 patients where slides were still available. The histological material was graded as either well differentiated or poorly differentiated/anaplastic.

Life-table analysis and survival curves were calculated to 10 years and comparison of patient survival was by the log-rank test (Peto et al, 1977).

RESULTS

The overall crude survival at 5 years was 20% and includes deaths from intercurrent disease (Fig. 1). If only patients who had received a radical dose of radiation (*i.e.* 50 Gy and above) are included, this crude survival rate rises to 25% at 5 years.

Fifty-four patients died of their disease, nine patients died of unrelated disease, and six patients died of a second primary malignancy. Sixteen patients were alive at the time of analysis and two patients were lost to follow-up (both known to be alive and free of disease at 8 years).

The effect of TNM classification on survival was assessed in three respects. Comparisons were made for different T stages, different N stages, and for combination of T and N. As no patients presented with distant metastasis it was unnecessary to include this in our analysis.

Effect of tumour size (T)

The overall survival and recurrence-free survival of T_1 tumours (Fig. 1) was better than that of other tumours ($p < 0.001$). There was no significant difference in survival between T_2, T_3, and T_4 tumours, but the number of T_4 lesions was small.

Effect of nodal status (N)

The overall survival and the recurrence-free survival rates showed that with increasing nodal status (N_0 to N_3) patient survival deteriorated ($p = 0.001$) (Fig. 2). Comparison of patients with nodal status N_0 and N_1 showed no statistical difference for survival; neither did comparison of N_2 patients with N_3 patients. When combining patients with N_0 and N_1 and comparing their survival with the combined group of patients with nodal status N_2 and N_3 (Fig. 3) the difference was statistically significant for overall survival ($p = 0\ 001$).

Effect of tumour and node status combined (T and N)

For T_1 and T_2 tumours, N_0 and N_1 have similar survival curves (Fig. 4).

Sites of treatment failure

In 24 patients the disease was never controlled by radiotherapy (Table II). All of these had T_2 to T_4 lesions, usually with advanced nodal involvement.

Loco-regional recurrence of disease occurred in 32 other patients; in 10 of these patients tumour recurred in the tonsillar fossa, in 12 patients cervical metastatic adenopathy occurred and in 10 patients tumour recurrence was manifest simultaneously in the neck and

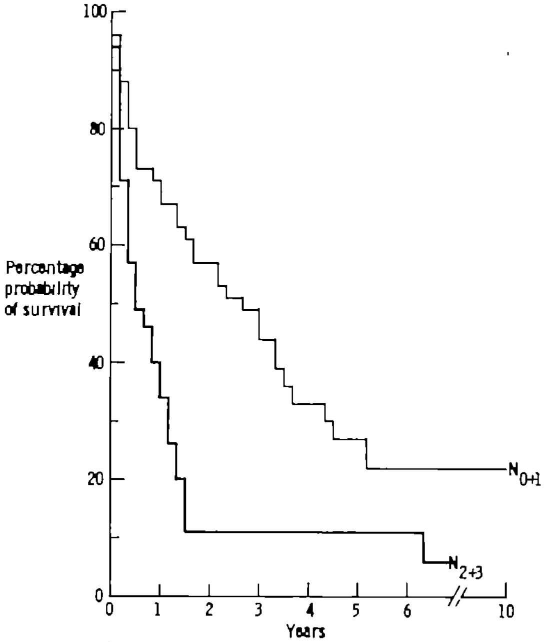

FIG. 3

Comparative survival of $N_{0,1}$ with $N_{2,3}$ including deaths by intercurrent disease.

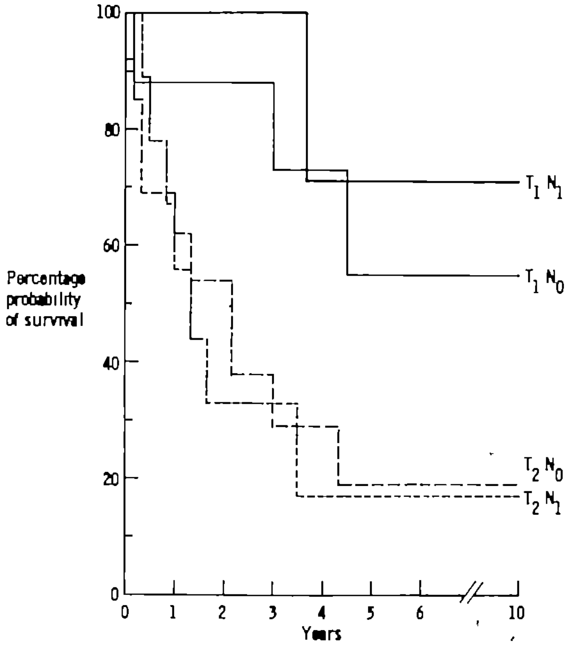

FIG. 4.

Survival of smaller tumours by combined T and N stage, including deaths by intercurrent disease.

in the tonsillar fossa. Significantly, in those patients where recurrent tumour was evident in only one site initially, the other site was later involved in approximately 50% of patients.

In four patients, evidence of failure of tumour control was found distant to the treated site, this metastasis being to lung, liver (two patients) and lumbar spine. Distant metastasis was also recorded in four other patients who had clinical evidence of loco-regional tumour recurrence, this being to the lung in two patients and intracranially in two patients. No recurrence was seen in 27 patients who either died of unrelated illness or were alive at analysis.

Second primary malignancy

Eleven patients during follow-up after treatment developed a second primary malignancy. In three patients this occurred in the contralateral tonsil, in two

TABLE II

PATIENT'S CLASSIFICATION: RELATIONSHIP OF TUMOUR CONTROL TO TNM STAGING

		Site of first recurrence				
Patient's TNM	Never controlled	Tumour T	Node N	Tumour/Node T/N	Metastases M	Tumour-free
T_1N_0	0	1	1	1	1	6
T_1N_1	0	0	0	1	0	3
T_1N_{2+3}	0	1	0	0	1	0
T_2N_0	2	0	2	3	1	5
T_2N_1	2	1	2	1	0	3
T_2N_{2+3}	7	2	2	3	1	3
T_3N_0	2	0	1	1	0	2
T_3N_1	1	3	2	0	0	2
T_3N_{2+3}	5	2	0	0	0	3
T_4N_0	0	0	0	0	0	0
T_4N_1	1	0	0	0	0	0
T_4N_{2+3}	4	0	2	0	0	0

TABLE III

SURGICAL SALVAGE AND OUTCOME

Patient	Surgical procedure	Post-operative survival	Disease status at death
1	Block dissection	6 months	Recurrent tonsil
2	Block dissection	6 months	"Carcinomatosis"
3	Block dissection	6 months	Ca. oesophagus (NED)
4	Block dissection	12 months	"Carcinomatosis"
5	Block dissection	30 months	"Carcinomatosis"
6	Block dissection	42 months	Pulmonary embolus (NED)
7	"Commando" procedure	11 years	Alive and well
8	"Commando" procedure	12 months	Alive and well

patients in the lung, in two in the oesophagus, in two in the lower gastrointestinal tract and in two in the genitourinary system. Six of these patients died from these second malignancies.

Further treatment after failure

"Salvage" therapy was employed in 25 patients. Eight patients had a surgical procedure (Table III), eight patients had further radiotherapy and nine patients received chemotherapy (nine different regimens).

Age and sex

Neither age nor sex was shown to have prognostic significance in terms of survival.

Histological review

All sections showed squamous-cell carcinoma: 28% of these were found to be well differentiated and 72% to be poorly differentiated/anaplastic. Histological grading of cell differentiation did not have a significant effect on survival.

DISCUSSION

The overall survival of patients who had a squamous-cell carcinoma of the tonsil treated in Nottingham by radiotherapy alone is poor (20% 5-year survival) but comparable with results obtained elsewhere (Mantravadi et al, 1978; Petrovich et al, 1980; Oreggia et al, 1983; Nofal, 1984). Of the deaths recorded, approximately 80% are directly attributable to the carcinoma. This perhaps reflects both the age of the population and the frequent late presentation of patients. Age, sex and histological grade did not have a significant effect on prognosis.

The TNM classification for disease status was an important prognostic indicator. Small (T_1) tumours of clinical stages N_0 and N_1 do well with radiotherapy alone. Nearly all of these patients were alive at 5 years or died in the interim of intercurrent disease with no signs of recurrence. Advanced tumours (T_2 and above) of clinical stages N_0 and N_1 have a small, but real, chance of cure. The prognosis for advanced tumours with extensive nodal involvement is poor. Radiotherapy alone as the treatment of choice for carcinoma of the tonsil has been widely accepted, but disappointing results for larger tumours have prompted renewed interest in combination surgery and radiotherapy (Perez et al, 1976). The finding that T_1 tumours carried a significantly better prognosis is in agreement with current literature.

This study found that nodal status N_0 and N_1 carry an equal survival while N_2 and N_3 carry a poor prognosis. This is in agreement with the findings of other series (Cardinale & Fischer, 1977; Doyle et al, 1978; Petrovich et al, 1980; Oreggia et al, 1983) but progressive worsening of prognosis with increasing N stage has also been noted (Givens et al, 1981; Perez et al, 1982). Occult nodal metastasis is reported to occur in 10–45% of clinically negative necks (Barrs et al, 1979; Givens et al, 1981) and single glands may be reactionary rather than containing tumour deposits. This may explain the similar survival for N_0 and N_1. The significance of nodal disease is emphasised by a finding of palpable neck nodes at presentation in 65% of patients.

Routine aspiration cytology might help to distinguish between those nodes that are involved and those that are not. Perhaps dividing N_1 into N_{1A} (one mobile gland) and N_{1B} (multiple mobile glands) might be prognostically useful.

Recurrence of disease after initial treatment is mainly due to failure of local control. Forty per cent of these patients showed evidence of tumour recurrence at the primary site alone, 20% in the neck alone and 40% in the primary site and neck simultaneously. Furthermore, in this series patients who showed tumour recurrence either at the primary site or in cervical nodes were found frequently to develop tumour recurrence at the other site at a later date. Thus, when considering salvage surgery for any recurrent disease, it would seem prudent to resect both the primary tumour site and cervical nodes in continuity.

In this series, analysis of the small number of patients (eight) who received salvage surgery revealed that two thirds of those having nodal resection alone died with recurrent disease in the tonsillar fossa, the remaining third dying of intercurrent disease. The two patients having resection of both primary site and neck nodes are alive with no signs of recurrence at 1 year and 11 years after surgery, respectively.

The role of surgery in the primary treatment of squamous-cell carcinoma of the tonsil remains controversial. No randomised trial of radiotherapy alone against either surgery alone or combination radiotherapy and surgery exists. The largest non-randomised study available fails to show any advantage for combined pre-operative radiotherapy (30 Gy) and surgery over radiotherapy alone (Perez et al, 1982). Other papers reviewing a group of patients receiving combination radiotherapy and surgery did not show an improvement in results over published figures for radiotherapy alone (Maltz et al, 1974; Weichert et al, 1976; Quenelle et al, 1979).

The major controversy lies around the role of combination radiotherapy and surgery for intermediate tumours, *i.e.* $T_{2,3}N_{0,1}$. As shown, the results for radiotherapy alone are only fair and the introduction of new flap techniques, such as myocutaneous flaps and free flaps, has reduced the late surgical morbidity (Ariyan & Cuono, 1980).

Unfortunately, the mortality rate associated with surgical management remains high (Givens et al, 1981; Perez et al, 1982) and, as the majority of patients who present with tonsillar tumours have nutritional and cardiorespiratory problems, it has been suggested that the addition of surgery may, at best, improve survival by 10% (Kaplan et al, 1977). As the prognosis for large tumours with extensive nodes is dismal, these should be dealt with on an individual basis.

It follows that planning of treatment of patients who present with a squamous-cell carcinoma of the tonsil should be undertaken in a joint clinic, involving both the radiotherapist and a surgeon. Accurate tumour staging and classification should be made and, ideally, all patients should be examined and biopsied under general anaesthetic, with aspiration cytology of all palpable cervical adenopathy

The value of histological grading of cell differentiation has long been disputed, having been shown in some series to be a good prognostic index (Fleming et al, 1976; Mantravadi et al, 1978) and not a useful prognostic index in others (Cardinale & Fischer, 1977; Perez et al, 1982; Oreggia et al, 1983). Our material was graded into either well differentiated or poorly differentiated/anaplastic. It was hoped that two-point categorisation would provide more useful information on survival than separate categories of well differentiated, moderately differentiated, poorly differentiated and anaplastic. Failure to do so may be explained by the fact that the state of differentiation may vary from section to section in the same biopsy or tumour (Nussbaum et al, 1983).

In conclusion, conventional radiotherapy produces good results for small primary tumours (T_1), in which extensive neck-node involvement is rare. Those advanced tumours ($T_{2,3}$) without advanced neck involvement ($N_{0,1}$) fare only moderately; for these lesions other treatments (*e.g.* innovative fractionation or combined-modality therapy) require prospective evaluation. Advanced tumours associated with heavy infiltration of the neck ($N_{2,3}$) have a dismal prognosis; improved results for such tumours will be difficult to achieve.

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Dose–response relationships for photodynamic injury to murine skin

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ABSTRACT

Oedema and necrosis of murine tail skin have been measured after intravenous injection of haematoporphyrin derivative ("Photofrin", or PhI) followed 24 h later by graded exposures of the tail to full-spectrum visible light from a quartz-halogen lamp. End-points were degree of oedema and the proportion of mice in a dose-group that developed skin necrosis and tail atrophy Oedema developed within 24 h of illumination and was a function of PhI dose and duration of light exposure Onset of necrosis occurred after a minimum of 5 days and onset time was an inverse function of exposure time. Probit plots of proportion of necroses versus light exposure yielded values for ND_{50} (exposure corresponding to 50% incidence of necrosis) and 1/slope At the high but non-toxic dose of 2 mg PhI/mouse, ND_{50} was 18 min, 1/slope 4 min, for pigmented BDF_1 mice Halving the PhI dose increased ND_{50} by a factor of 1.9. Albino BALB/c mice were markedly more sensitive to 2 mg PhI plus light than BDF_1 mice: the ND_{50} was 7 min Temporary occlusion of the blood supply to the tail (10 min before and during illumination) abrogated totally the oedematous and necrotic reactions to photodynamic therapy.

In photodynamic therapy (PDT) two agents that are of themselves relatively non-toxic (visible light and light-absorbing molecules such as porphyrins), in combination produce highly-reactive chemical species that can damage biologically important molecules and cause cell death (reviewed recently by Spikes, 1984). Light-delivery systems that permit localised illumination (Doiron, 1984), and longer retention of some porphyrins by tumours than normal tissues (*e.g* Fioretti et al., 1984), provide the major rationales for use of PDT as an anti-cancer modality.

Little is known of the quantitative relationships of porphyrin and light on injury to normal tissues, although such damage is likely to determine the therapeutic efficacy of PDT. With current clinically used forms of PDT, acute injury to skin manifested as oedema and in severe cases necrosis, has been observed (*e.g.* Kennedy & Oswald, 1984). We present here initial results for a murine model of injury to skin that enables quantitation of oedema and necrosis as a function of dose of porphyrin and exposure to light.

MATERIALS AND METHODS

Male mice of three strains were used at a mean weight of 25 g (±1.5 g SD). Two strains were pigmented: $B6D2F_1$ ("BDF_1" = C57BL6 × DBA/2) and DBA/2; and one was albino: BALB/c.

The photosensitising drug employed was haematoporphyrin derivative ("Photofrin", or PhI; Photofrin Medical, New York*). This is a mixture of several porphyrin species produced by acetic acid-sulphuric acid treatment of the dihydrochloride of the naturally occurring compound haematoporphyrin (*e.g* Bonnett et al, 1981; Dougherty et al, 1984). The drug was diluted where necessary in saline to yield a constant injection volume of 0.4 ml, and was injected as a single bolus intravenously at the tip of the tail The dark colouration of PhI permits immediate recognition of local extravasation; animals in which this occurred were not used. Preliminary results for intraperitoneal injection will not be described in detail here, but do not appear to be greatly different from those for intravenous injection. Injections were made between 10.00 and 11.00 h.

A 12 V, 100 W quartz-tungsten-halogen lamp ("Xenophot HLX"; Wotan, London) was used for illumination with a KG1 infra-red filter (Schott, Mainz). This set-up produced light within the wavelength band 300–1100 nm. Peak spectral irradiance occurred at approximately 700 nm. Less than 10% of the total irradiance was due to light of wavelength below 400 nm and greater than 900 nm. Optical lenses were employed to produce a circular light beam with uniform irradiance across a 2.5 cm diameter (fall-off from the centre to the edge of the beam was 10%). Power density in air at the working distance of 25 cm from the lamp, was 75 mW/cm² of white light.

There were six mice in each experimental group. Most experiments were repeated once and in these cases the data were pooled. Mice that had received either PhI or saline alone were kept in the dark for 24 h before illumination. This interval was chosen as being on a "plateau" of concentration of haematoporphyrin derivative in the skin of DBA/2 mice (Gomer & Dougherty, 1979). The mice were then lightly restrained without anaesthesia, and positioned such that the central portion of the tail lay across a diameter of the light beam (the injection site for the drug lay outside the beam). The tails received single exposures of 5–120 min QH light. Temperature on the skin surface during illumination was monitored by a thermocouple. In most experiments, dermal temperature was measured for one animal per group by introducing a second thermocouple via a 25-gauge syringe needle. In one set of experiments the influence of blood supply was measured by applying a rubber clamp 10 min before and during illumination; controls received either PhI plus the clamp, clamp plus light only, or clamp only. The clamp was released immediately after illumination. In all experiments, mice were returned to the dark for 24 h and subsequently housed in subdued lighting conditions. Longer periods of post-retention in the dark have been investigated but the results were not different from those for the present 24 h regime. Oedema of the tail was calculated for different intervals after illumination by placing the tail in a mercury column and measuring the displacement of mercury. The incidence of gross necrosis was measured by a method previously used for ionising radiation (Hendry, 1978), in terms of the proportion of mice in a treatment group for which the tail atrophied and was lost distally to the front edge of the light beam.

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*The supply of this compound from this source has been discontinued The biologically active fraction of haematoporphyrin derivative, described as dihaematoporphyrin ether ("Photofrin II"), is supplied by Photofrin Medical Inc, US Route 202, Raritan, NJ 08869, USA.

RESULTS

Dermal temperature of the murine tail is normally close to ambient (20–22°C in the present experiments). Within 5 min of onset of illumination at 75 mW/cm^2, dermal temperature in mice that had received either PhI or saline rose to approximately 29°C and thereafter remained constant (± 1°C).

In a first set of experiments, three logarithmic dilutions of PhI were injected into BDF$_1$ mice: 0.02 mg, 0.2 mg and 2.0 mg/mouse. These doses were non-lethal and did not cause torpor. At 0.02 mg, no oedema occurred with light exposures between 10 min and 40 min (three representative times are shown in Fig. 1). At 0.2 mg, transient oedema that commenced at 1 day and resolved by 5 days, occurred at exposures of 30 min or more. At 2.0 mg, an average twofold increase in tail volume was observed for all exposures down to 10 min.

In subsequent experiments, necrosis of tails in BDF$_1$ mice occurred reproducibly when the dose of PhI exceeded 0.5 mg/mouse. Time of onset of necrosis varied inversely with time of light exposure (Fig. 2, left panel). The longest time to necrosis was 28 days, the minimum 5 days. This form of injury is non-stochastic in that, for each dose of PhI, there was a threshold light exposure below which necrosis did not occur (Fig. 2, right panel). Above this threshold, incidence of necrosis increased as a steep function of dose. Data were analysed by a probit-fitting program (Gilbert, 1969). At 2.0 mg PhI, the ND$_{50}$ (light exposure time for 50% incidence of necrosis) was 17.8 min (SE ± 1.1 min). The reciprocal of the slope of the fitted probit curve (which represents the standard deviation of the distribution and which equals the time for incidence to increase from 16% to 50% or from 50% to 84%) was 4.5 ± 1.1 min. At 1.0 mg of PhI, ND$_{50}$ increased to 34.6 ± 1.2 min, 1.9 times higher than for 2 mg. Reciprocal slope was 6.3 ± 1.7 min. At 0.5 mg, there was extremely wide variation in response within and between repeated experiments (although all mice had oedematous reactions) and a satisfactory curve for necrosis could not be obtained.

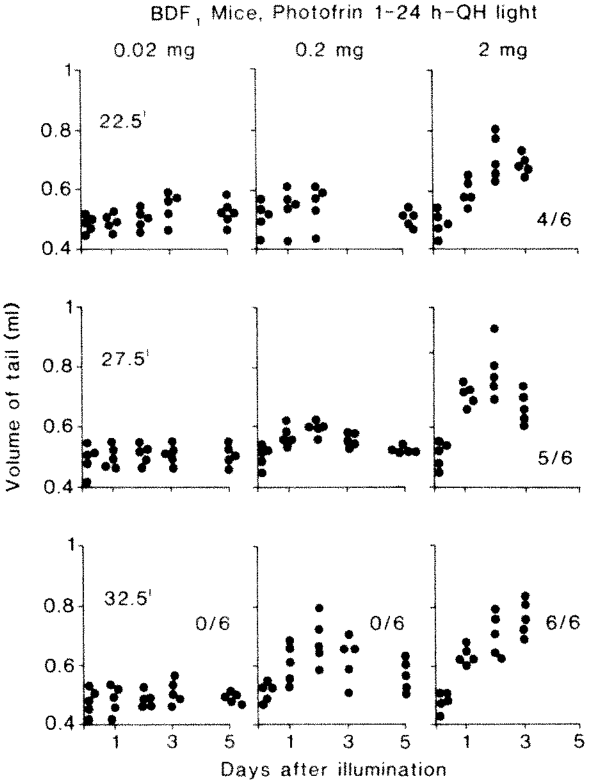

FIG. 1.

Degree of oedema measured in terms of whole tail volume, as a function of dose of Photofrin I (0.02 mg, 0.2 mg, 2.0 mg/mouse), three representative times of illumination (22.5 min, 27.5 min, 32.5 min) and time after illumination. Data points are for individual mice. Proportion of mice in a group showing necrosis between 5 and 30 days is given as 0/6, 4/6 etc.

At 2.0 mg of PhI, range of times of onset of necrosis was the same for BALB/c (Fig. 2, left panel) and DBA/2 as for BDF$_1$ mice. The ND$_{50}$ and reciprocal slope of the curve of incidence of necrosis for the pigmented DBA/2 mice, were only insignificantly different from those for BDF$_1$ (15.6 ± 1.1 min, 5.5 ± 1.2 min; Fig. 3, left panel). However, the ND$_{50}$ for the albino BALB/c was significantly lower, at 7.4 ± 3.2 min ($p < 0.05$). Scatter on the data points was somewhat greater for the BALB/c mice, yielding a high inverse slope of 10.3 ± 4.4 min.

Occlusion of the blood supply for 10 min prior to and

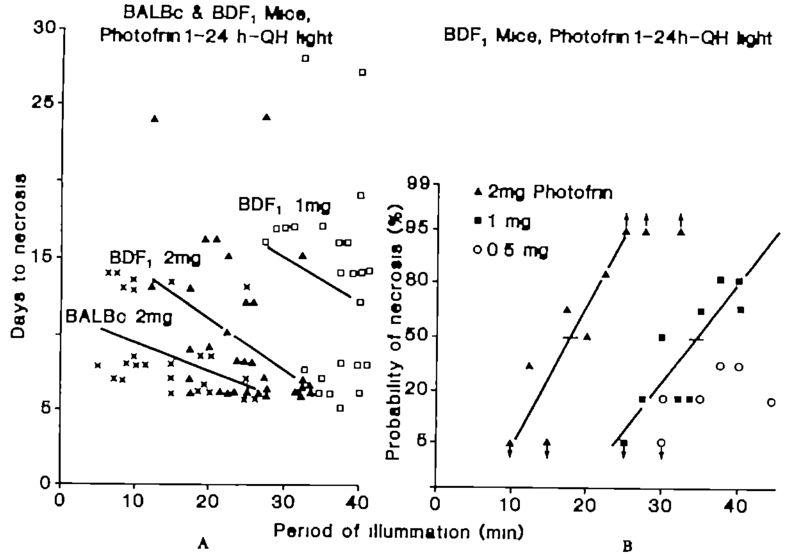

FIG. 2.

(A) Time at which tail atrophied, as a function of duration of illumination for BDF1 mice (□, 1 mg/mouse of PhI; △, 2 mg/mouse) and BALB/c mice (×, 2 mg/mouse). (B) Probability of tail necrosis (probability ordinate) as a function of duration of illumination, for three different doses of PhI.

during illumination totally abrogated the oedematous and necrotic reactions of BDF$_1$ mice for exposure times up to 110 min (Fig. 3, right panel). At 120 min exposure, a 20% incidence of necrosis was observed but this was not preceded by oedema. As necrosis occurred also in all the control groups at this time (including clamp alone, no PhI, no QH light), it was believed to represent a non-photodynamic, ischaemic necrosis.

DISCUSSION

This study has demonstrated for an experimental system, that PDT may result in non-stochastic injury to skin, that is, for a given dose of porphyrin, characterised by a threshold time of illumination and a subsequently steep increase in incidence of necrosis with exposure time. In this respect, the outcome of PDT resembles that for ionising irradiation of murine skin (Hendry, 1978) and other normal tissues in animals and man (*e.g.* Moore et al, 1983). The only other PDT dose-incidence study of which we are aware, is for acute "brain death" in mice (Rounds et al, 1984). From their data, it can be calculated that the ratio of reciprocal slope to ND$_{50}$ (which is one measure of the "criticality" of the prescribed dose), was as little as 12% to 25%, comparable to or less than those that we have found for skin. Precise comparisons cannot be made between these two sets of results because of differences in the large number of variables that determine the final biological outcome of PDT; for example, mouse strain, wavelength and power density of light, and dose of photosensitising drug.

PhI has a strong absorption band in the near-UV and a number of only weak absorption bands in the visible

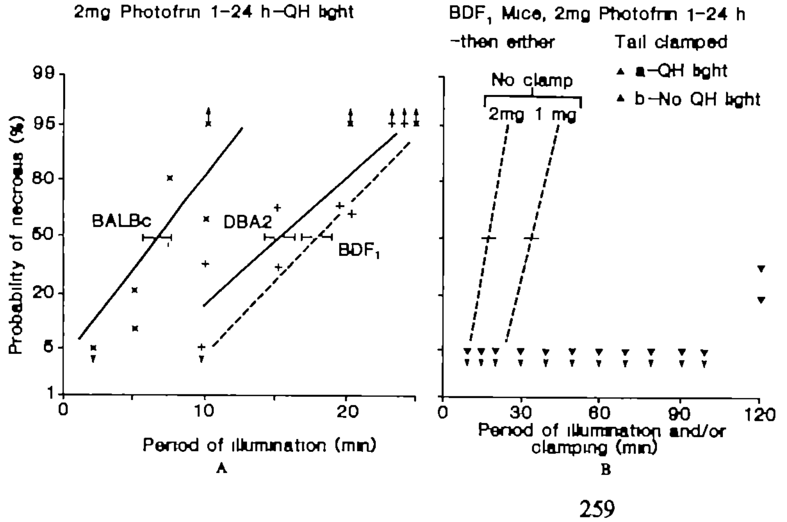

FIG. 3.

(A) Probability of tail necrosis as a function of duration of illumination, for BDF$_1$ mice (dashed line, from Fig. 2B), DBA/2 mice (+), or BALB/c mice (×) (B) Probability of tail necrosis as a function of duration of illumination, for 1 mg or 2 mg/mouse of PhI plus light, with the tail blood supply unimpeded (dashed lines, from Fig 2B), or for 2 mg/mouse with the blood supply occluded 10 min before further treatment. The control shown here (▽) is for PhI plus clamp without QH light; similar results were obtained for clamp plus light alone without PhI, and for clamp alone without PhI or light.

range, of which the 630 nm band has been widely used for laser applications of photodynamic therapy. The relatively poor absorption of tissue-penetrating, red light by PhI has led to the investigation of other compounds with stronger absorption in this wavelength region, such as phthalocyanins and chlorins. In the present study, the "effective" incident power density will have been considerably less than the 75 mW/cm^2 that we have quoted. Also, attenuation of the shorter wavelengths within the epidermis means that the (mostly red) light reaching the dermis may have been at very low power density relative to that used by Rounds et al (1984): 319 mW/cm^2 of 631 nm light incident on the scalp surface. Accordingly, in these early experiments, to achieve the end-points we have had to use doses of PhI considerably higher (but still non-toxic) than that in the study by Rounds et al (0.15 mg/mouse). However, it is of interest that Bonnett et al (1984) have suggested that a dose of haematoporphyrin derivative of 40 mg/kg (= 1 mg/mouse in the present study) should be approximately equivalent, in terms of surface area, to a dose of 3 mg/kg in man, which is a dose commonly used in the clinic (*e.g.* Carruth & McKenzie, 1985). If this suggestion is correct, then the doses of PhI used here to achieve skin necrosis are not "unrealistic".

Unlike ionising radiation, for which the time of onset of skin reactions and necrosis is virtually independent of radiation dose (*e.g.* Hendry, 1978), time of onset after PDT was an inverse function of exposure time (Fig. 2, left panel). Skin necrosis after ionising radiation is believed to be a consequence of severe primary injury to cells of the epidermis, with damage being expressed (after approximately 2 weeks) when pre-existing, radiation-resistant differentiated cells complete their transit of the epithelium in the normal time but are not replaced (Potten, 1981). Photodynamic therapy leaves the epidermis initially relatively intact, injury being manifested through an early dermal oedema (Fig. 1) and rapid degradation of the dermal microvasculature (Bickers, 1983).

The response to PDT more closely resembles that to hyperthermia, with onset of tail necrosis varying as an inverse function of exposure and occurring after only a few days for longer exposures (Morris et al, 1977). High power densities of visible light do result in heating of tissue to temperatures greater than 37°C (*e.g* Kinsey et al, 1983). This is not thought to have contributed significantly to the present results because (a) at the incident power density of white light used (75 mW/cm^2), dermal temperature never exceeded 31°C, either for PhI-treated mice or light-alone treatments, and (b) the effect of clamping rodent tails and applying hyperthermia (> 37°C) is to *sensitise* the tissue (Morris et al, 1977), quite unlike the profound sparing seen with PDT (Fig. 3, right panel). This sparing of cells made acutely hypoxic by clamping, consistent with the involvement of oxygen in photodamage *in vivo*, has led several workers to speculate on whether chronically hypoxic tumour cells might be similarly spared. However, as the tumour microvasculature on which tumour growth depends, is promptly ($\leqslant$ 1 day) and massively damaged by PDT (Star et al, 1984) the precise response of the dependent parenchyma may be less important than for ionising radiation.

Strategies have been developed in clinical PDT for minimising the probability of normal tissue injury, notably by allowing sufficient time to elapse between injection of the porphyrin and exposure to light, for clearance of the drug from the normal tissue while it is still retained by the tumour. Using PhI, a fixed interval of 3 days is very commonly employed, for different tumours in different sites (*e.g.* Carruth & McKenzie, 1985). We suggest that monitoring of levels of photosensitising drugs should be an important consideration in the development of PDT, for once thresholds (whose size depends on both drug and light exposures) are exceeded, then the incidence of injury to normal tissue may well rise as a steep function of further exposure.

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Book review

Radiation Protection (Protocol for X-ray Dosimetry EULEP) A European Commission Report. By J. Zoetelief, J. J Broerse and R. W Davies, pp. 98, 1985 (Commission of the European Communities), £4.60.
ISBN 92–825–4575–X

Beware—titles are not always a good indication of content! The report is entitled "Radiation Protection (Protocol for X-ray Dosimetry)" and this may lead the uninitiated to think that the topic covered was X-ray dosimetry methods in radiation protection. The key letters to the title page are "EULEP". This is an acronym for European Late Effects Projects Group, and the present protocol from the Group is an updated version of a 1972 edition intended to serve as a manual for X-ray dosimetry and exposure arrangements for radiobiological studies in small experimental animals. As such it is a very good guidebook, containing a lot of basic X-ray dosimetry. It will be most valuable to a radiobiologist seeking to standardise exposure conditions and dosimetry in order to obtain valid and comparable data.

The protocol itself occupies less than a quarter of the report and includes recommendations on irradiation conditions, dosimetry requirements, and basic X-ray dosimetry concepts. This section concludes with a Code of Practice for X-irradiation of small animals. The remainder of the report contains 10 useful supplements describing irradiation procedures employed by the participating institutes and the results of five X-ray dosimetry intercomparisons. The latter shows that the variation from a standards laboratory calibration was commonly over 5%, which emphasises the need for a dosimetry protocol such as this.

This should be a very useful report for every radiobiologist who wishes to improve on his dosimetry methods or simply wishes to check his methods against the suggested protocol.

S. C. Lillicrap

1986, *The British Journal of Radiology*, 59, 263–270 MARCH 1986

Tumour uptake of radiolabelled pyrimidine bases and pyrimidine nucleosides in animal models IX. Radiolabelled 1-(2′-fluoro-2′-deoxy-*β*-*D*-ribofuranosyl)uracil and 1-(2′-chloro-2′-deoxy-*β*-*D*-ribofuranosyl)uracil

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ABSTRACT

The biodistribution of radiolabelled 1-(2′-fluoro-2′-deoxy-*β*-*D*-ribofuranosyl)uracil (2′-FUdR) and 1-(2′-chloro-2′-deoxy-*β*-*D*-ribofuranosyl)uracil (2′-ClUdR) was evaluated using *in-vivo* and *in-vitro* tumour models. 6-[^{3}H]-2′-FUdR exhibited a maximum tumour · blood (T : B) ratio (Walker 256 carcinosarcoma) of 1.0 at 15 min after injection whereas 2-[^{14}C]-2′-FUdR and 2′-[^{36}Cl]-2′-ClUdR exhibited maximum T : B ratios (Lewis lung carcinoma) of 3.0 and 4.1 respectively at 120 min. Clearance of blood radioactivity after injection of 6-[^{3}H]-2′-FUdR, 2-[^{14}C]-2′-FUdR and 2′-[^{36}Cl]-2′-ClUdR was rapid and best described by a biexponential function. The clearance half-lives of the short-lived components were calculated as 1.6 min (95.5%), 2.3 min (94.7%) and 1.2 min (96.0%) respectively. The clearance half-lives of the long-lived components were 23 h (4.5%) for 6-[^{3}H]-2′-FUdR, 89 min (5.3%) for 2-[^{14}C]-2′-FUdR, and 49 min (4.0%) for 2′-[^{36}Cl]-2′-ClUdR. Less than 36% of the ^{14}C radioactivity present in the urine 2 h after injection of 2-[^{14}C]-2′-FUdR was associated with 2′-FUdR, whereas greater than 91% of the ^{36}Cl radioactivity in the urine 2 h after injection of 2′-[^{36}Cl]-2′-ClUdR was associated with 2′-ClUdR. Both 6-[^{3}H]-2′-FUdR (< 3.1 pmol/10^6 cells) and 6-[^{3}H]-2′-ClUdR (1.0 ± 0.2 pmol/10^6 cells) were incorporated into cultured Raji tumour cells *in vitro* to a lesser extent than the natural nucleosides uridine (137.2 ± 3.8 pmol/10^6 cells) and 2′-deoxyuridine (23.5 ± 2.5 pmol/10^6 cells) after a 20 min incubation.

The biological activity of pyrimidine nucleoside analogues is related to their ability to act as substrates for membrane transport and enzymes in the various biosynthetic pathways. For example, a number of C-5 radiohalogenated pyrimidine nucleosides, which are thymidine analogues, have shown diagnostic and therapeutic potential in oncology (Bloomer & Adelstein, 1975; Robins & Taylor, 1981). These analogues, such as ^{131}I-labelled 5-iododeoxyuridine (5-[^{131}I]-IUdR), have demonstrated significant uptake in tissues with high mitotic index, including the intestinal epithelium, bone marrow and some tumours. However, a major disadvantage of the use of these C-5 labelled pyrimidine nucleoside analogues is that they are rapidly dehalogenated *in vivo* (Barrett & West, 1956). This dehalogenation results in low tissue utilisation of the labelled nucleoside and high background blood levels of circulating radiohalide anion (Kriss et al, 1963).

In view of the disadvantages of the C-5 labelled nucleoside analogues, some C-6 (Abrams et al, 1984; Lee et al, 1984a), C-3′ (Lee et al, 1984b,c) and C-2′ (Lee et al, 1979a,b; Abrams et al, 1981) radiohalogenated nucleoside analogues have been synthesised as new radiotracers with potentially greater stability to *in vivo* dehalogenation. The 2′-halo-2′-deoxyuridine analogues, in which the 2′-hydroxyl function has been replaced with a fluorine or chlorine atom in the ribose configuration, are structurally related to 2′-deoxyuridine but are considered to be conformational analogues of uridine (Cushley et al, 1968; Guschelbauer & Jankowski, 1980). Although the biochemical fate of the 2′-halo-2′-deoxyuridine analogues is not well understood, it is known that 2′-FUdR and 2′-ClUdR are substrates for the nucleoside transport system of the red blood cell, which is blocked by nitrobenzylthioinosine (NBMPR) (Gati et al, 1983). They are therefore able to enter the cell and interact with the cellular metabolic processes. We have evaluated the *in vivo* tissue distribution of 6-[^{3}H]-2′-FUdR, 2-[^{14}C]-2′-FUdR and 2′-[^{36}Cl]-2′-ClUdR in murine tumour models. In addition, the *in vitro* uptake of the complete series of C-2′ halogen-substituted uridine nucleosides, including 2′-[^{82}Br]-2′-BrUdR and 2′-[^{125}I]-2′-IUdR, for which the *in vivo* uptake of both have been reported previously (Lee et al, 1976b; Abrams et al, 1981), was determined in cultured Raji tumour cells.

EXPERIMENTAL

Radiochemicals

6-[^{3}H]-2′-FUdR (4.26 GBq/mmol; 115 mCi/mmol), 2-[^{14}C]-2′-FUdR (1.86 MBq/mmol; 50 μCi/mmol) and 2′-[^{36}Cl]-2′-ClUdR (5.66 MBq/mmol; 153 μCi/mmol) were synthesised for the tissue distribution studies as described by Abrams et al (1985). The radiochemical syntheses of 6-[^{3}H]-2′-ClUdR (11.1 GBq/mmol,

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†Address for enquiries and offprints.

300 mCi/mmol), 2′-[^{82}Br]-2′-BrUdR (1.83 MBq/mmol; 49 μCi/mmol) and 2′-[^{125}I]-2′-IUdR (2.72 GBq/mmol; 73 mCi/mmol) for the *in vitro* Raji-cell uptake studies were described previously (Lee et al, 1979a; Abrams et al, 1981). The radiotracers were purified by silica-gel thin-layer chromatography (TLC) on Whatman MK6F* plates or by reverse-phase high pressure liquid chromatography (RP-HPLC) using a C_{18} μBondapak* (3.9 mm in diameter, 30 cm in height) column. The radiochemical purity of each compound was confirmed by radio-TLC and radio-RP-HPLC in several solvent systems.

Sample preparation and analysis

The radiolabelled nucleosides were dissolved in sterile normal saline and filtered through a 10 μm Millipore* filter prior to injection.

Biological samples containing ^{3}H, ^{14}C and ^{36}Cl were prepared using standard techniques. Beta-ray emitting samples were counted on either a Berthold BF500* or a Beckman LS9000* automatic liquid scintillation spectrometer. All samples were dark-adapted and temperature-equilibrated before counting. Gamma-ray emitting samples were analysed on a Tracor 2200* or a Beckman 8000* gamma spectrometer.

Animal preparation

The Lewis lung carcinoma (LLCa) tumour model was maintained as a solid tumour in young adult (20–25 g) male BDF$_1$ hybrid mice. The tumours were used 8 to 10 days after implantation and ranged from 100 mg to 300 mg in size. The tumour-bearing mice were prepared by subpannicular implantation of a fragment of the solid tumour into the right flank region of the recipient animal, as described previously (Lee et al, 1984a).

The Walker 256 carcinosarcoma tumour model was maintained in young male Wistar rats (200–250 g) as a solid tumour. The recipient rats were inoculated in the right hind-leg muscle group with approximately 10^7 cells, 5 to 7 days before the experiment, as described previously (Lee et al, 1984a).

Tissue distribution

Each animal was anaesthetised with ether, exsanguinated by cardiac puncture, and sarcificed by cervical dislocation at various time intervals after injection of the radiolabelled compounds. The tissues of interest were excised in their entirety, blotted free of blood, and weighed. The muscle-tissue samples consisted of specimens from the front and rear muscle groups of the hind leg (contralateral to the tumour-bearing leg in the rats). The femur from the same leg was taken as the bone sample. Skin samples were obtained from the back of the animal to decrease the possibility of radioactive contamination from the urine during handling. The whole organ, or aliquots thereof, was prepared for specific analysis, as described, for each compound.

6-[^{3}H]-2′-FUdR

Five male Wistar rats bearing Walker 256 carcinosarcomas were used at each time period. Each rat was injected intravenously with 0.15 MBq (4 μCi) of 6-[^{3}H]-2′-FUdR (3.5 pmol) in 0.4 ml normal saline via the tail vein. Aliquots of each tissue (approximately 100 mg) were accurately weighed directly in glass liquid scintillation counting (LSC) vials, solubilised (2.0 ml Soluene-350*, Packard), and if necessary decolourised with 30% hydrogen peroxide. The solubilised samples were then dissolved in 15 ml of fluor (4 g PPO and 50 mg/l POPOP in toluene) for LSC analysis.

2-[^{14}C]-2′-FUdR

For each time period six BDF$_1$ male mice bearing LLCa were injected intravenously with 55 kBq (1.5 μCi) of 2-[^{14}C]-2′-FUdR (0.029 μmol) in 0.1 ml normal saline. Aliquots (approximately 100 mg) of the tissues of interest were prepared for LSC by oxidation with a Harvey OX300 Biological Oxidizer*. Urine samples at each time period were pooled and lyophilised. The lyophilised product was extracted with methanol (0.5 ml) containing authentic 2′-FUdR, 2′-UdR, uracil and uridine as reference compounds. The extract was analysed by reverse-phase TLC (upper phase of ethyl acetate : *n*-propanol : water, 4 : 1 : 2 by volume, diluted with ethyl acetate, 8 : 1 by volume). The chromatographic bands containing the components of interest and "blank" plate sections were visualised with ultraviolet light, removed from the plate, and directly extracted with water in LSC vials. Fifteen millilitres of Biofluor* (New England Nuclear) was added to the extracted samples which were then analysed by LSC.

2′-[^{36}Cl]-2′-ClUdR

Six male BDF$_1$ mice bearing LLCa were studied at each time interval. Each mouse was injected intravenously with 7.78 kBq (0.2 μCi) of 2′-[^{36}Cl]-2′-ClUdR (1.37 μmol) in 0.1 ml normal saline. The entire heart, lungs, spleen, kidney, testicle, tibia and femur, and aliquots of tumours, muscle and liver were weighed directly in glass LSC vials, wetted with distilled water (0.2 ml) and solubilised (2.0 ml NCS*, New England Nuclear). The samples were dissolved in 15 ml Riafluor* (New England Nuclear) and neutralised with a mixture of 4% aqueous SnCl$_2$ and acetic acid (1 : 1 by volume) prior to counting. Blood samples were lysed with distilled water, digested in NCS* and decolourised with 30% hydrogen peroxide prior to counting in Riafluor*.

The entire bladder and its contents were excised and aliquots (5 μl) of the urine were analysed directly, using silica-gel TLC and chloroform : ethanol (2 : 1 by volume) as the solvent system. The chromatographic plates were analysed as described for 2-[^{14}C]-2′-FUdR.

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*Trade mark

Blood clearance kinetic parameters

Whole-blood radioactivity versus time data were analysed using the University of Alberta "Nonlin" curve-fitting computer program to obtain the blood clearance curves.

In vitro *Raji cell culture uptake studies*

Raji cells (10^7 cells/ml) were suspended in RPMI growth medium (GIBCO) supplemented with 10% fetal calf serum, HEPES (25 mM) buffer and glutamine. The radiolabelled 2'-halo-nucleosides (6-[^{3}H]-2'-FUdR, 6-[^{3}H]-2'-ClUdR, 2'-[^{82}Br]-2'-BrUdR and 2'-[^{125}I]-2'-IUdR) and reference nucleosides (6-[^{3}H]-uridine and 6-[^{3}H]-2'-deoxyuridine) were diluted with unlabelled carrier to prepare 0.13 mM solution in Dulbecco's phosphate buffered saline (PBS).

Uptake experiments in triplicate were initiated by the addition of 0.5 ml of the appropriate radiotracer (kept at 37°C) to the Raji cell suspension. The final radiotracer concentration was 10 μM. Cell uptake was terminated by transferring 1.0 ml of the cell suspension to 0.4 ml of ice-cold PBS in a 1.5 ml Eppendorf centrifuge tube. The contents of each tube were quickly mixed on a vortex mixer and centrifuged, and the supernatant fluid was removed by vacuum aspiration. The cell pellet was then washed with four 1 ml aliquots of ice-cold PBS and transferred quantitatively in two 0.5 ml aliquots of distilled water to 10 ml Aquasol-2 (New England Nuclear) for analysis by LSC.

RESULTS

The tissue distribution of ^{3}H and ^{14}C labelled 2'-FUdR was studied in male Wistar rats inoculated with Walker 256 carcinosarcomas and in BDF$_1$ mice bearing LLCas respectively. The liver and kidneys rapidly accumulated radioactivity after intravenous injection of 6-[^{3}H]-2'-FUdR (3.5 pmol per rat) and accounted for greater than 32% and 3% of the injected dose per organ, respectively, 15 min after injection. The blood contained 5% of the radioactive dose after 15 min and this level remained constant during the six-hour period studied. The remaining tissues examined, including the tumour, gave no evidence for accumulation of 6-[^{3}H]-2'-FUdR or its radiolabelled metabolites. The tissue : blood ratios for these tissues remained constant at each time period studied, indicating that blood perfusion, rather than tissue uptake, accounted for the majority of the radioactivity observed in the tissues. Tumour : blood ratios (Table I) at no time exceeded one and were comparable, within experimental error, with the values calculated for the spleen and gastrointestinal tract (GIT).

The tissue distribution of ^{14}C radioactivity after injection of 2-[^{14}C]-2'-FUdR into BDF$_1$ mice bearing LLCas, differed from the distribution of ^{3}H after injection of 6-[^{3}H]-2'-FUdR. The short-lived component of the whole-blood clearance curves (Fig. 1) for ^{3}H and ^{14}C were similar ($T_{\frac{1}{2}}$ = 1.6 and 2.3 min respectively) but the long-lived components differed considerably ($T_{\frac{1}{2}}$ = 23 h and 89 min respectively). The liver and kidney uptake of ^{14}C (5.7 and 4.9% of the injected dose per organ respectively), as was observed for ^{3}H, accounted for a large proportion of the injected dose 15 min after injection. However, the tumour, GIT and spleen also demonstrated high levels of ^{14}C radioactivity (1.1%, 5.5% and 2.2% respectively), which was not observed for 6-[^{3}H]-2'-FUdR. The tumour : tissue ratios of ^{14}C (Table II) for all tissues except the GIT and spleen tended to increase with time. The tumour : GIT and tumour : spleen ratios remained constant. This is consistent with active uptake of the ^{14}C label into the cellular nucleic-acid pool of proliferating cells.

The urine radioactivity was analysed by TLC to estimate the extent of metabolism of 2-[^{14}C]-2'-FUdR at each time period studied (Table III). Catabolism of 2-[^{14}C]-2'-FUdR was slow, with 63% of the urinary ^{14}C activity associated with unmetabolised 2'-FUdR 15 min after injection, and 23–32% remaining 240–360 min after injection. The large proportion of 2'-deoxyuridine in the urine was an unexpected observation. The formation of such a large amount of 2'-deoxyuridine,

TABLE I

DIFFERENTIAL DISTRIBUTION OF RADIOACTIVITY IN WISTAR RATS BEARING WALKER 256 CARCINOSARCOMAS AFTER INTRAVENOUS INJECTION OF 6-[^{3}H]-2'-FUdR

Tissue	Ratio of tumour radioactivity to tissue radioactivity					
	15 min	30 min	60 min	120 min	240 min	360 min
Blood	1.00±0.10	0.87±0.08	0.82±0.17	0.69±0.15	0.62±0.13	0.76±0.10
Liver	0.11±0.03	0.17±0.07	0.27±0.06	0.68±0.15	0.65±0.09	0.73±0.27*
Kidney	0.16±0.04	0.19±0.02	0.30±0.07	0.56±0.08	0.63±0.02	0.74±0.19
Muscle	1.35±0.11	1.30±0.12	1.23±0.36	1.41±0.47	1.33±0.23	1.07±0.13
Bone	1.84±0.24	2.01±0.40	1.82±0.70	1.78±0.60	2.04±0.70	2.16±0.36
Skin	0.97±0.41	1.12±0.41	1.27±0.16	1.05±0.28	1.26±0.42	1.37±0.31

*n = 4

Data are expressed as the mean values of the ratio of tumour : tissue concentrations of radioactivity ± SD (n = 5) at various time intervals following injection.

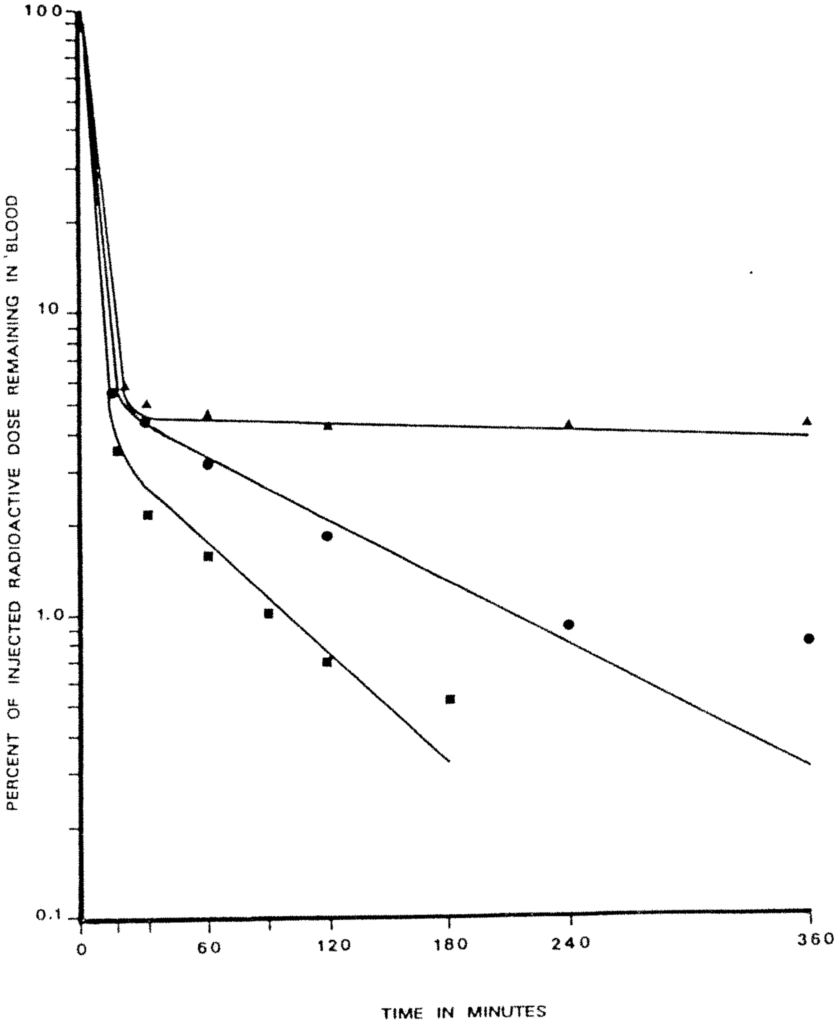

FIG. 1.

Whole-blood clearance of 2′-FUdR and 2′-ClUdR. The data were fitted, using the University of Alberta "Nonlin" curve fitting program, to biexponential curves for each nucleoside. The $T_{\frac{1}{2}}$ and fraction cleared in each component were:

6-[^{3}H]-2′-FUdR (▲) $T_{\frac{1}{2}} = 1.6$ min (95.5%) and 23 h (4.5%), 2-[^{14}C]-2′-FUdR (●) $T_{\frac{1}{2}} = 2.3$ min (94.7%) and 89 min (5.3%), 2′-[^{36}Cl]-2′-ClUdR (■) $T_{\frac{1}{2}} = 1.2$ min (96.0%) and 49 min (4.0%).

relative to the other components, from 2-[^{14}C]-2′-FUdR is difficult to explain via known chemical or biochemical pathways.

The differential tissue-distribution studies of 2′-[^{36}Cl]-2′-ClUdR were conducted using male BDF$_1$ mice bearing a subpannicular LLCa as the tumour model. The injected radioactivity (7.78 kBq; 0.2 μCi per mouse) was rapidly removed from the blood with less than 1% of the dose remaining 2 h after injection. The whole-blood clearance curves were resolved into biexponential functions. The $T_{\frac{1}{2}}$ of the short-lived component was 1.2 min (96%) and of the long-lived component was 49 min (4%). The liver (3.6% of the injected dose per organ at 15 min), spleen (2.1%), kidney (1.2%), gastrointestinal tract (4.1%) and tumour (2.4%) were the chief organs to take up ^{36}Cl. The tumour : tissue ratios (Table IV) for most tissues rose during the time intervals studied, indicating selective trapping of ^{36}Cl by the tumour. The tissue : blood ratios for the tumour, kidney and spleen increased during the first hour after injection and remained high for the duration of the experiment.

TABLE II

DIFFERENTIAL DISTRIBUTION OF RADIOACTIVITY IN BDF$_1$ MICE BEARING LEWIS LUNG CARCINOMAS AFTER INTRAVENOUS INJECTION OF 2-[^{14}C]-2'-FUdR

Tissue	Ratio of tumour radioactivity to tissue radioactivity 15 min	30 min	60 min	120 min	240 min	360 min
Blood	1.55±0.15	1.90±0.20	2.18±0.46	3.04±0.53	3.00±0.56	2.58±0.34
Liver	1.54±0.17	1.96±0.23	2.18±0.48	2.97±0.54	2.26±0.77*	2.59±0.27
Spleen	0.27±0.03	0.30±0.07	0.30±0.07	0.38±0.10	0.39±0.08	0.38±0.07
Kidney	0.50±0.17	0.69±0.13	0.73±0.17	0.92±0.22	1.32±0.87	1.11±0.30
GIT	1.44±0.08	1.71±0.24	1.73±0.25	2.23±0.41	2.18±0.29	1.81±0.35
Stomach	1.89±0.26	2.41±0.43	2.59±0.58	3.23±0.53	2.69±0.84	2.67±0.53
Muscle	1.57±0.12	1.96±0.22	2.14±0.49	2.91±0.62	2.63±0.53	2.48±0.44
Bone	1.97±0.20	2.39±0.22	2.75±0.46	3.68±0.92	3.25±0.48	2.91±0.46
Skin	1.76±0.14	2.16±0.24	2.87±0.81	3.44±0.74	3.04±0.76	3.24±0.68

*$n = 4$

Data are expressed as the mean value of the ratio of tumour : tissue concentrations of radioactivity ± SD ($n = 5$) at various time intervals following injection

Determination of the total amount of radioactivity present in the urinary bladder at each time period and chromatographic analysis of the urine contained in the bladder at the time of sacrifice allowed the extent and nature of metabolism of 2'-[^{36}Cl]-2'-ClUdR to be estimated (Table V). Most of the injected radioactive dose (70%) was recovered in the urine within 3 h after injection. It cannot be assumed that the urine collected represented the total amount formed during the period studied, and therefore these values underestimate the true rate of excretion. It is, however, evident that 2'-[^{36}Cl]-2'-ClUdR was rapidly excreted unchanged in the urine. Catabolism of 2'-[^{36}Cl]-2'-ClUdR occurred slowly. The 3 h urinary analysis indicated that 85% of the excreted radioactivity was still associated with unmetabolised 2'-ClUdR.

An *in vitro* experiment was performed to determine the extent of incorporation of the 2'-halo-2'-deoxyuridine analogues by cultured Raji tumour cells. 2'-ClUdR (1.0±0.2 pmol/10^6 cells) and 2'-IUdR (2.9±0.3 pmol/10^6 cells) were incorporated to a lesser extent than were 6-[^{3}H]-uridine (137.2±3.8 pmol/10^6 cells) and 6-[^{3}H]-2'-UdR (23.5±2.5 pmol/10^6 cells) after a 20 min incubation. Neither 2'-[^{82}Br]-2'-BrUdR nor 6-[^{3}H]-2'-FUdR demonstrated uptake within the limits of detection (71 and 3.1 pmol/10^6 cells respectively) of the experiment.

DISCUSSION

2'-FUdR and 2'-ClUdR are conformational analogues of uridine and are therefore expected to behave similarly (biochemically) to uridine. For example, both 2'-FUdR and 2'-ClUdR are substrates for an erythrocyte nucleoside transport mechanism (Gati et al, 1983). In addition, the phosphorylated species of 2'-FUdR were shown to be substrates of *Escherichia coli* thymidylate synthetase and polynucleotide phosphorylase (Pinto et al, 1979) and RNA

TABLE III

RADIOACTIVE URINARY EXCRETION PRODUCTS AFTER INTRAVENOUS INJECTION OF 2-[^{14}C]-2'-FUdR into BDF$_1$ MICE BEARING LEWIS LUNG CARCINOMAS

Time (min) post injection	% of urinary radioactivity associated with: 2'-FUdR	2'-UdR	Uracil	Uridine	Unidentified*
15	63.2	17.1	—	—	19.7
30	38.9	37.4	13.2	—	10.6
60	37.5	38.2	18.4	2.9	2.9
120	36.0	7.8	4.2	16.4	35.8
240	22.2	28.1	28.4	6.4	14.6
360	32.3	32.5	29.5	—	5.6

*% urinary ^{14}C not associated with 2'-FUdR, 2'-UdR, uracil and uridine.

The results were determined by reverse-phase thin-layer chromatographic analysis of the urine collected at each time interval. Data are expressed as the mean value (duplicates) of the pooled samples at each time interval.

TABLE IV

DIFFERENTIAL DISTRIBUTION OF RADIOACTIVITY IN BDF$_1$ MICE BEARING LEWIS LUNG CARCINOMAS AFTER INTRAVENOUS INJECTION OF 2′-[^{36}Cl]-2′-ClUdR

Tissue	Ratio of tumour radioactivity to tissue radioactivity					
	15 min	30 min	60 min	90 min	120 min	180 min
Blood	2.19±0.56	3.11±0.94	3.54±1.24	3.92±1.18	4.09±0.67	4.09±1.82
Heart	1.48±0.30	2.57±0.62	3.03±0.46	3.32±1.05*	3.22±0.73	2.93±1.14
Lungs	1.63±0.44	2.37±0.66	3.12±0.89	3.20±0.78*	2.75±0.70	2.55±1.31
Liver	1.81±0.62	2.89±0.66	3.31±0.51	3.59±1.24	3.44±0.68*	3.38±1.07
Spleen	0.32±0.06	0.29±0.06	0.36±0.11	0.42±0.26	0.42±0.15	0.34±0.11
Kidney	0.64±0.11	1.01±0.33	1.21±0.32	1.27±0.39	1.73±0.40*	1.08±0.38
Testes	2.40±1.06	2.65±0.76	1.98±0.44	1.90±0.34	3.40±0.82*	2.30±1.41
GIT	1.32±0.66	1.98±0.32	1.92±0.90	2.20±0.48	2.55±0.75	2.03±0.71
Stomach	2.27±0.53	3.02±0.41	3.54±1.14	3.24±0.92	3.92±1.00	3.10±0.59
Muscle	2.07±0.40	2.74±0.96	3.15±1.24	3.07±1.35	4.33±0.70	3.35±1.69
Bone	2.72±1.12	3.86±1.08	4.53±0.64	3.13±0.51*	4.27±1.22	2.92±1.76
Skin	1.78±0.52	2.43±0.67	3.16±1.31	2.31±0.14*	3.68±1.16	2.89±0.91

*$n = 4$

Data are expressed as the mean value of the ratios of tumour : tissue concentrations of radioactivity ± S.D. ($n = 5$) at various time intervals following injection.

polymerase (Janik et al, 1972) while the diphosphate of 2′-ClUdR was reported to be a substrate of *Micrococcus lysodeikticus* polynucleotide phosphorylase (Hobbs et al, 1972).

The liver (32% after 15 min) and kidney (3.4%) were the major organs involved in uptake and excretion of the ^{3}H injected as 6-[^{3}H]-2′-FUdR into rats bearing Walker 256 carcinosarcomas. The short-lived component of the blood-clearance data ($T_{\frac{1}{2}} = 1.6$ min) accounted for 95.5% of the 6-[^{3}H]-2′-FUdR injected, and the remaining 4.5% was cleared slowly with a $T_{\frac{1}{2}}$ of 23 h. This was consistent with the behaviour of 5-[^{3}H]-uridine, which was reported to be rapidly degraded (70–90%) in the liver on the first pass (Gasser et al, 1981; Moyer et al, 1981) and to exhibit a constant level of blood radioactivity up to 4 h after injection. The major metabolites of 5-[^{3}H]-uridine were 5-[^{3}H]-uracil and [^{3}H]-water (Moyer et al, 1981).

Tissues other than the liver and kidney exhibited tissue : blood ratios of one or less. This is consistent with the tissue distribution of a substrate which is freely membrane-permeable, such as [^{3}H]-water, which could arise *in vivo* via metabolic or chemical exchange processes. This, however, could also describe the behaviour of 2′-FUdR since 2′-FUdR is readily transported by the human erythrocyte nucleoside

TABLE V

RADIOACTIVE URINARY EXCRETION PRODUCTS AFTER INTRAVENOUS INJECTION OF 2′-[^{36}Cl]-2′-ClUdR INTO BDF$_1$ MICE BEARING LEWIS LUNG CARCINOMAS

Time (min) post injection	% of urinary radioactivity associated with.			
	% of injected dose recovered in urine*	^{36}Cl-chloride	2′-[^{36}Cl]-2′-ClUdR	Unidentified†
15	12.7± 6.5	2.3±2.4	95.0±2.9	2.5±3.0
30	31.1±14.5	6.5±2.9	88.1±4.4	7.1±4.3
60	42.7±30.4	2.4±1.3	92.0±4.8	5.5±4.2
90	53.3±18.2	3.2±1.3	90.8±3.4	6.0±3.4
120	56.3±18.2	3.2±1.3	90.8±3.4	6.0±3.4
180	69.7±10.6	4.8±5.0	85.3±6.0	9.7±5.5

*Includes the urinary bladder and contents removed from each mouse during dissection and represents the total radioactivity excreted into the urine during the time period in question minus the urinary activity excreted before sacrifice

†% of urinary ^{36}Cl unaccounted for by ^{36}Cl chloride and 2′-[^{36}Cl]-2′-ClUdR.

The results were determined by silica-gel thin-layer chromatographic analysis of the urine collected at each time interval. Data are expressed as the mean value ± standard deviation ($n = 5$) at each time interval

TABLE VI

Tumour index of the 2′-halo-2′-deoxyuridine analogues calculated according to the method of Emrich et al (1972)

Nucleoside		15	30	60	90	120	180	240	360	480	720	960	1440
		Time after injection (min)											
6-[^{3}H]-2′-FUdR	mean	0.31	0.24	0.19	—	0.13	—	0.10	0.15	—	—	—	—
	± SD	0.06	0.05	0.08	—	0.05	—	0.05	0.04	—	—	—	—
2-[^{14}C]-2′-FUdR	mean	8.80	10.47	8.05	—	9.16	—	4.76	3.45	—	—	—	—
	± SD	3.48	1.71	2.71	—	2.86	—	1.66	1.96	—	—	—	—
2′-[^{36}Cl]-2′-ClUdR	mean	10.00	13.13	10.96	8.76	8.82	6.08	—	—	—	—	—	—
	± SD	4.39	5.85	5.46	3.94	3.55	4.09	—	—	—	—	—	—
2′-[^{82}Br]-2′-BrUdR	mean	1.55	1.23	2.05	—	2.66	—	3.30	—	—	4.26	—	2.07
(Lee et al, 1979)	± SD	0.77	0.15	0.74	—	0.68	—	0.90	—	—	2.31	—	0.17
2′-[^{125}I]-2′-IUdR	mean	1.90	2.99	2.50	—	2.01	—	0.75	—	0.26	—	0.016	0.002
(Abrams et al, 1981)	± SD	0.22	0.52	0.63	—	0.93	—	0.46	—	0.01	—	0.008	0.002

Data are the product of the tumour : blood ratios and the % dose incorporated per g of tumour and are expressed as the mean value ± S.D. ($n = 5$) at each time interval.

transport mechanism (Gati et al, 1983), and was recently shown not to be phosphorylated by either thymidine kinase or uridine-cytidine kinase (Gati et al, in press). This suggests that although 2′-FUdR is a permeant of all cells capable of transporting the natural nucleosides, it may not be metabolically trapped by phosphorylation. 6-[^{3}H]-2′-FUdR would therefore be freely membrane-permeable and exhibit a tissue distribution profile similar to that of [^{3}H]-water. In addition, cultured Walker 256 carcinosarcoma cells have an atypical nucleoside transport mechanism which is relatively insensitive to nitrobenzylthioinosine inhibition (Paterson et al, 1983). The tumour model therefore appeared to be inappropriate for testing nucleoside radiotracers and the probability that the long-term tissue distribution data represented both 6-[^{3}H]-2′-FUdR and [^{3}H]-water derived from 6-[^{3}H]-2′-FUdR led us to reassess the uptake of 2′-FUdR using 2-[^{14}C]-2′-FUdR in a different tumour model (LLCa).

The tissue distribution data and the blood clearance curves for 2-[^{14}C]-2′-FUdR were similar to the 2′-[^{36}Cl]-2′-ClUdR data but differed from the 6-[^{3}H]-2′-FUdR results. The tumour : tissue ratios for 2-[^{14}C]-2′-FUdR and 2′-[^{36}Cl]-2′-ClUdR suggested selective trapping or uptake of ^{14}C and ^{36}Cl in the spleen and tumour relative to the other tissues. The 2-[^{14}C]-2′-FUdR data supported the hypothesis that tritium was an inappropriate radiolabel for *in vivo* studies of this nucleoside.

Cellular uptake of natural nucleosides requires transport across the membrane followed by subsequent phosphorylation to trap the nucleoside metabolically against a concentration gradient. If metabolic trapping does not occur, the intracellular nucleoside concentration can only reach equilibrium with the extracellular concentration. The cultured Raji cell uptake curves of 2′-[^{125}I]-2′-IUdR and 6-[^{3}H]-2′-ClUdR equilibrated rapidly, reaching their maximum concentration in the cells within 30 s. In contrast, both 6-[^{3}H]-uridine and 6-[^{3}H]-2′-deoxyuridine were incorporated into Raji cells in a linear fashion over a prolonged period. The observed uptake data indicated that the Raji cells were unable to accumulate the halogenated nucleosides due to an inability either to transport the nucleosides into the cells or to trap the nucleosides metabolically. This would be in keeping with *in vitro* studies of these compounds using the erythrocyte nucleoside transporter and isolated mammalian pyrimidine kinases (Gati et al, in press).

The value of a tumour delineating agent is determined by its tumour specificity, which is a function of the absolute amount of radioactivity in the tumour, and the ratio of the radioactivity in the tumour to that in the blood and surrounding tissues. Both of these parameters are dynamic, changing with time after injection. One measure of this specificity, the tumour index (Emrich et al, 1972), is the product of the tumour uptake (% injected dose incorporated per g tumour) and the tumour : blood ratio. The tumour indices for these nucleoside analogues and the bromo- and iodo-analogues tested previously (Lee et al, 1979b; Abrams et al, 1981) are also given in Table VI. Based on the tumour index, appropriately labelled 2′-ClUdR and 2′-FUdR would be the better tumour imaging agents for the nucleosides in this series, and the best time for imaging would be between 15 and 30 min for 2′-ClUdR and between 30 and 120 min for 2′-FUdR. These times are compatible with the use of ^{34}Cl^{m} and ^{18}F ($T_{\frac{1}{2}}$ 32 min and 110 min respectively), the only suitable radionuclides for scintigraphic imaging studies of these compounds.

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Technical notes

The effect of temperature on ultrasonic images in infant cadavers

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Parents of a deceased infant are sometimes reluctant to allow a complete autopsy. Ultrasonic examination of a cadaver may therefore be a useful, non-invasive alternative, which can examine either the brain, or the abdominal organs, in attempting to establish a post-mortem diagnosis.

Cadavers may be used both in research (Cremin and Draper, 1981) and to compare ultrasonic appearances with pathologic findings. During the course of such a cadaver study, investigating infant cerebral oedema, it was noted that the quality of the ultrasonic images was adversely affected by the low temperatures of the cadavers. The effect on attenuation of ultrasound in body tissues has been discussed in the technical scientific literature, but the high level of ultrasonic beam attenuation due to profound hypothermia is not otherwise widely known.

This communication therefore illustrates the effect of hypothermia on the ultrasonic brain images of infant cadavers, and it is hoped that identification and elimination of the cold artefact will be of use to other workers in this field.

MATERIAL AND METHOD

Neurosonic images were produced using an ATL Mk II 5 MHz rotating-head mechanical sector scanner. Fifteen infant cadavers who had died from a variety of causes were studied. The cadavers were refrigerated at −2°C within 1 h of death. Ultrasound scans were performed on the cadavers immediately before autopsy, up to 2 days after death, when core temperatures averaged 5°C.

Two cadavers were frozen solid due to refrigerator malfunction, and were excluded from the study. Eight showed no cerebral abnormality, and little or no histological evidence of autolysis was seen in brain sections. Of the five which showed cerebral pathology, four showed cerebral oedema (one of these also showed intraventricular bleeding), and one showed ventricular dilatation.

As the supply of cadavers was intermittent and could not be predicted, they were scanned during routine daily sessions at which live infants of the same ages were being examined. It was noted that an abnormally dark image was obtained with a bright, near field, and loss of brain tissue echoes in the mid and far fields. Considerable readjustment of the machine settings with an increase in gain of greater than 10% was usually required to obtain a satisfactory image in the cadaver as compared with the live infant (Fig. 1A,B).

The images obtained in one cadaver that had been allowed to warm to room temperature over several hours showed no significant difference from those obtained in live infants.

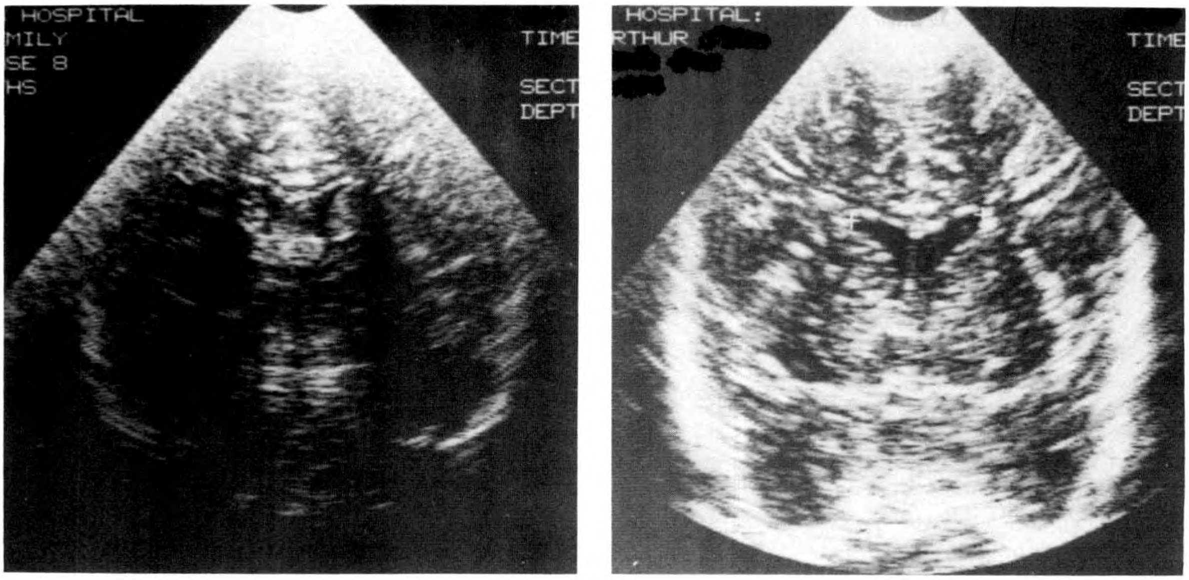
DISCUSSION

The attenuation coefficient (α) of ultrasound in soft tissues is a function of the frequency of the sound wave (f) and is related by the equation $\alpha = Af^b$ where A and b are constants which depend on the specific tissue characteristics and the conditions, such as temperature, under which the measurements were made. It has been found experimentally that α rises with decreasing temperature and increasing frequency, and that the magnitude of attenuation increases as temperature falls (Kremkau et al, 1976; Bamber and Hill, 1979). However, understanding of the complex properties involved in transmission and attenuation of the ultrasonic beam in mammalian tissue is poor (Wells, 1980).

Most experimental work on the temperature effects of transmission in human brain tissue has been performed on adult specimens, but measurements on infant brain tissue show attenuation levels of approximately one third of adult values (Kremkau et al, 1979). This has been attributed to the high infant-brain water content. Despite this difference, however, the physical concept of temperature dependence is presumably unaltered.

Factors such as the inclusion in the tissues of minute bubbles, due to the effect of post-mortem tissue deterioration, or the formation of ice crystals during cooling, may also change the tissue characteristics (Bamber et al, 1977), causing increased attenuation.

Previous reports concerning attenuation changes in tissue following excision at post-mortem are conflicting, and both increased (O'Donnell et al, 1979) and decreased (Kremkau et al, 1979) attenuation have been attributed to tissue degeneration. The finding of an apparently normal image in the one cadaver that was scanned after the temperature had risen to room



A B

FIG. 1.

Ultrasonic brain scan of a cold infant cadaver (A) compared with that of a normal live infant of the same age (B).

temperature is in no way conclusive, but suggests that temperature has a more significant effect on the image than tissue breakdown.

Although this study was designed for brain examinations, the cold artefact was incidentally noted in the solid organs of the abdomen.

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Technical notes

Development and assessment of an image intensifier for real-time X-ray microscopy

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This note describes a microchannel electron multiplier which has been modified from its intended application as a direct-viewing night-vision system to render it suitable as an image intensifier for X-ray microscopic studies. A micro-channel is a narrow tube of semiconducting lead glass, covered by a secondary electron emission layer. It operates by application of a potential of about 1000 V across the channel, producing a longitudinal electric field inside the tube. When an electron strikes the channel input, it generates two or three secondary electrons by colliding with the channel-plate walls. These electrons enter the electric field and after acceleration repeatedly strike the wall, producing further secondary electrons. The total gain of this multiplication process is usually of the order of 10^4 to 10^5. These tubes can be fused together to form a microchannel plate (MCP). The working principles of MCPs have been described in detail by Eschard and Manley (1971).

The need for an X-ray MCP image intensifier has been realised particularly in the field of crystallography (Arndt & Gilmore, 1979; Arndt, 1982). Other authors have considered their application in both industrial and medical X-ray imaging (Kuhl, 1973; Woodhead & Ward, 1977; Chalmeton, 1980). All the detectors described have the following basic components (Fig. 1):

(1) an X ray-to-electron converter,
(2) a MCP image intensifier,
(3) a coupling system between the image intensifier and a camera,
(4) a closed circuit television camera or spot film camera.

THE COMPONENTS OF THE IMAGE INTENSIFIER

The X-ray phosphor

An X-ray phosphor is required to convert X-ray photons to light photons. To achieve this polycrystalline gadolinium oxysulphide (Gd_2O_2S) with a particle size of 8 μm was layered on to one surface of a 25 mm diameter × 3 mm thick fibre-optic faceplate, to a density of 10 mg cm^{-2} (Arndt, 1982). The opposing face of the phosphor-coated optical fibre was sealed directly on to the surface of the input faceplate of the image intensifier using optical grease.

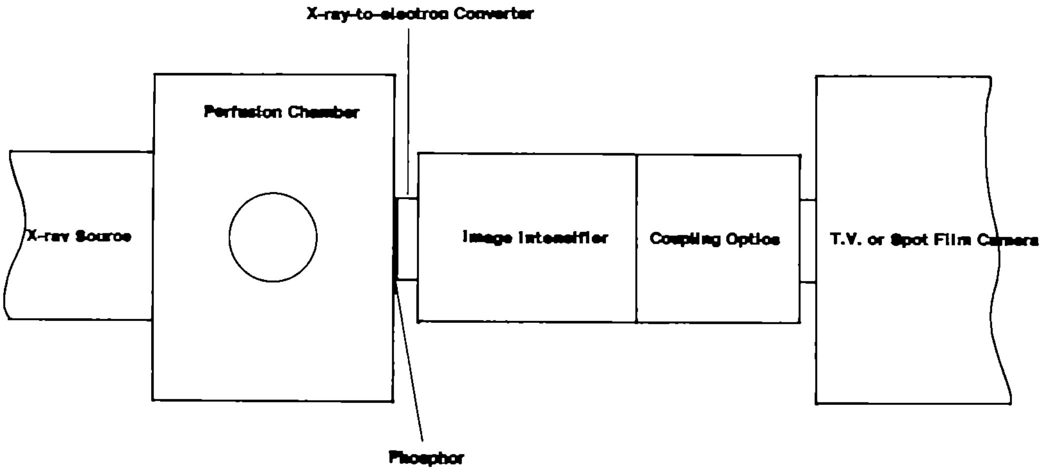


FIG. 1.
Component parts of the imaging system used for low energy X-ray microscopy.

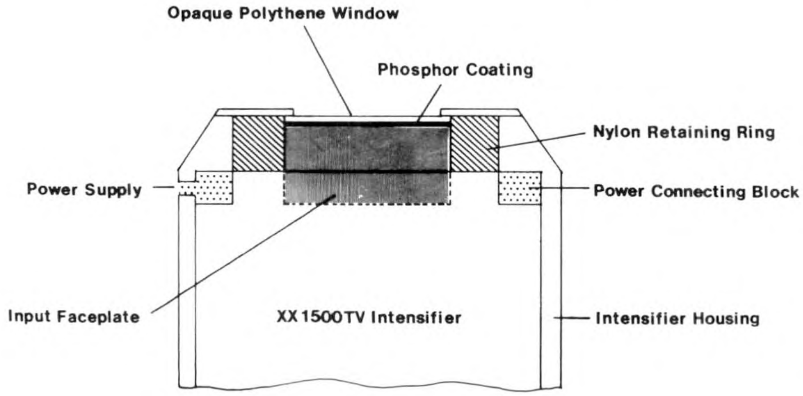


FIG. 2.

Modifications to the XX1500TV image intensifier housing. Note the retaining ring holding the phosphor-coated faceplate firmly in position.

The microchannel plate image intensifier

A Mullard XX1500TV add-on image intensifier (Alrad Instruments, Newbury) which incorporates a second generation electrostatically self-focused, inverting MCP image intensifier was used. An 18 mm fibre-optic input and output window, an integral power supply and an automatic gain control are incorporated into the intensifier, which is commercially available.

MODIFICATIONS

The front end of the image intensifier housing was modified (Fig. 2) to accept a nylon retaining ring which held the fibre-optic faceplate in position centrally over the input faceplate of the intensifier. A thin plastic mask on the latter faceplate was removed to ensure that it made intimate contact with the phosphor-coated faceplate. The electrical power-supply socket has to be removed and a cable brought out through the side of the housing to enable the power supply to be operated from behind the X-ray source. The gain was adjusted by an external potentiometer, included in the power supply, which controlled the potential across the plate walls. A thin layer of opaque polythene was stretched across the retaining ring which held the polythene 0.5 mm from the phosphor coating. The polythene window served to protect the phosphor coating and shield the intensifier from light photons. These modifications to the front end of the housing allowed the phosphor to be in very close contact with the specimen under investigation, thereby reducing geometrical blurring of the image.

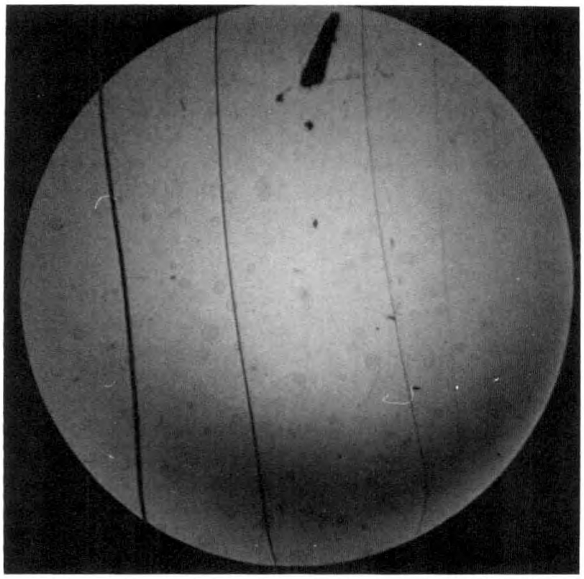


FIG. 3.

Image of four tungsten wires, 10, 25, 50 and 100 μm in diameter used to assess resolution.

Coupling between the intensifier and camera

A lens system (Alrad Instruments) was used to couple the closed-circuit television camera to the back of the image intensifier housing. A standard "C" type mount formed an integral part of the coupling lens. A similar lens system was used to connect a 35 mm camera to the back of the image intensifier housing.

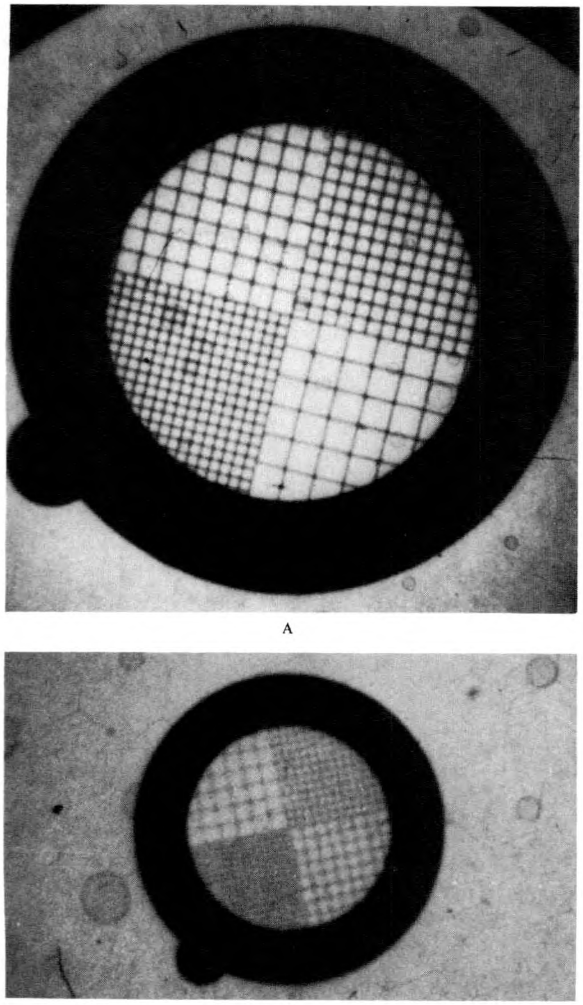
Cameras

A 2/3 inch Newvicon camera tube was used in a Koyo CCTV camera (Series TVC-5210). The camera was mounted on a laboratory jack to allow manipulation of the camera in the X-ray beam. The camera was connected through a U-matic video cassette recorder and two high resolution black and white monitors, one monitor being used for positive imaging, the other for negative imaging.

A 35 mm format Canon AE1 Program camera fitted with a data back and autowind was used for spot films, using Kodak 2415 film rated at 50 ASA.

APPLICATIONS

As the main application of this image intensifier is in X-ray microscopic studies, a microfocal and an X-ray



A

B

FIG. 4.

Images of gold Athene electron microscope grid of mixed mesh (150, 200, 300 and 400). The diameter of the grid is 3.05 mm, the bar widths are 10 μm. (A) A projection image of the grid at a primary magnification of × 22 (15 kV) using a microfocal X-ray source. (B) The same grid imaged using an X-ray diffraction unit (15 kV), shown here at a × 12 magnification. Note the loss of detail in the 400 mesh due to the larger focal-spot size of the X-ray diffraction tube.

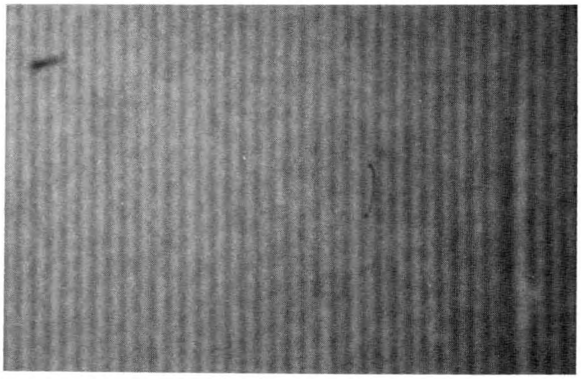


FIG. 5.

A projection image of a zone plate, photographed from the back of the intensifier, resolving 10 μm bars and spaces (100 line pairs per mm).

diffraction source were used to produce low energy X rays (< 30 kV). The assessment parameters of the image intensifier were established using gold Athene electron microscopy grids with bar widths of 10 μm, tungsten wires (Goodfellows Metals, Cambridge) 5, 10, 25, 50 and 100 μm in diameter, and a zone plate having a 10 μm bar and space width (Figs 3, 4 and 5). The resolution was markedly improved when the microfocal source was used (Fig. 4). The 5 μm diameter wire was resolved on both the monitor and video cassette using this source. By using the intensifier with CCTV camera at 30 cm from the X-ray source and a focus-to-specimen distance of 7.5 cm with primary magnification plus electronic magnification it was possible to produce a well defined image with up to 80 times enlargement.

At these low energies, conventional X-ray image intensifiers are unsuitable as they do not operate below 30 kV, and their large size makes them impractical for use with microfocal X-ray sources.

The image intensifier described here has been

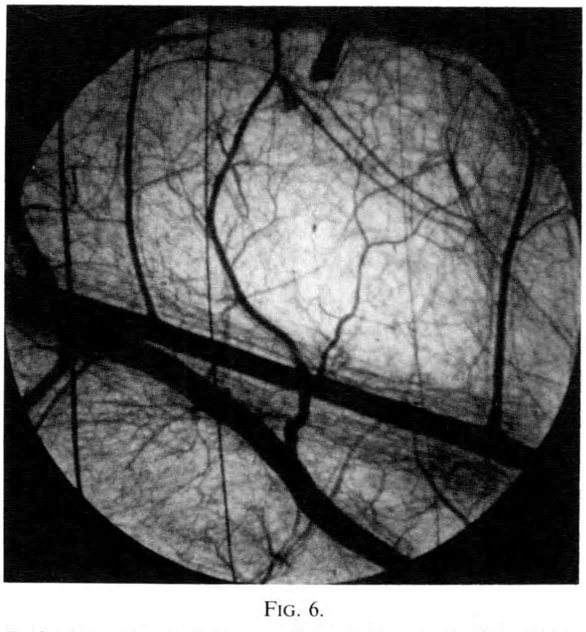


FIG. 6.

Projection microangiogram of a rabbit ear (× 20) photographed from the back of the intensifier (15 kV). The tungsten wires were used to compare the relative sizes of the vessels seen.

successfully used with X-ray sources operating in the range 3 to 140 kV and 10μA to 20 mA with horizontal or vertical beams. One application of this unit is for microangiographic studies using low energy X-radiation (3–25 kV). With beam currents of less than 250 μA it is possible to resolve images of contrast-filled blood vessels less than 15 μm in diameter in the rabbit ear (Fig. 6).

The results obtained show that the modifications to the MCP image intensifier described, have made it a compact and versatile unit, with a wide variety of applications.

ACKNOWLEDGMENTS

We would like to thank Mr A. Winters, Alrad Instruments Ltd, Newbury, for his assistance and comments and for arranging the loan of an image intensifier, and Mr K. Willison, Mullard House, Mitcham, Surrey for making available for assessment an image intensifier and fibre-optic faceplates. Our thanks are also due to Mr T. Harrison for his technical assistance and to Miss A Davies for typing the manuscript.

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Case reports

Gigantiform cementoma—an unusual incidental finding

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A cementoma is not an uncommon lesion to present in the jaws; the gigantiform variety is extremely rare. Reported cases are few, and hence available statistics are sparse. The lesion has been classified by Pindborg et al (1971) as a benign odontogenic lesion most commonly seen in middle-aged negroid females. The lesion may be familial (Agazzi & Belloni, 1953) but evidence for this is unconvincing.

Radiologically, the appearance of the gigantiform cementoma is characterised by lobulated areas of radiopacity occurring symmetrically in the premolar and molar regions of both the maxilla and mandible. The lesions are normally fused with the cementum of the adjacent teeth, although a case of gigantiform cementoma has been described in an edentulous subject (Punniamoorthy, 1980). The entity is probably truly neoplastic (Winer et al, 1972) and may expand within the jaw to cause facial deformity (Lucas, 1984).

We report a case of gigantiform cementoma occurring in the maxilla and the mandible that was discovered incidentally during routine radiological investigations.

CASE REPORT

A 45-year-old negroid female presented to the Department of Oral Surgery, having been referred by her general medical practitioner for the investigation of a painless swelling in the left floor of the mouth of 6 months duration.

The patient's past medical history was unremarkable apart from pulmonary sarcoidosis diagnosed 6 years previously, which was treated at the time with steroids. She had no symptoms for the past 4 years and was no longer taking medication.

Examination revealed a cystic swelling in the left floor of the mouth which was diagnosed as a ranula. An incidental finding at the time of examination showed that the patient had expansion of the right body of the mandible and a screening orthopantomogram was requested.

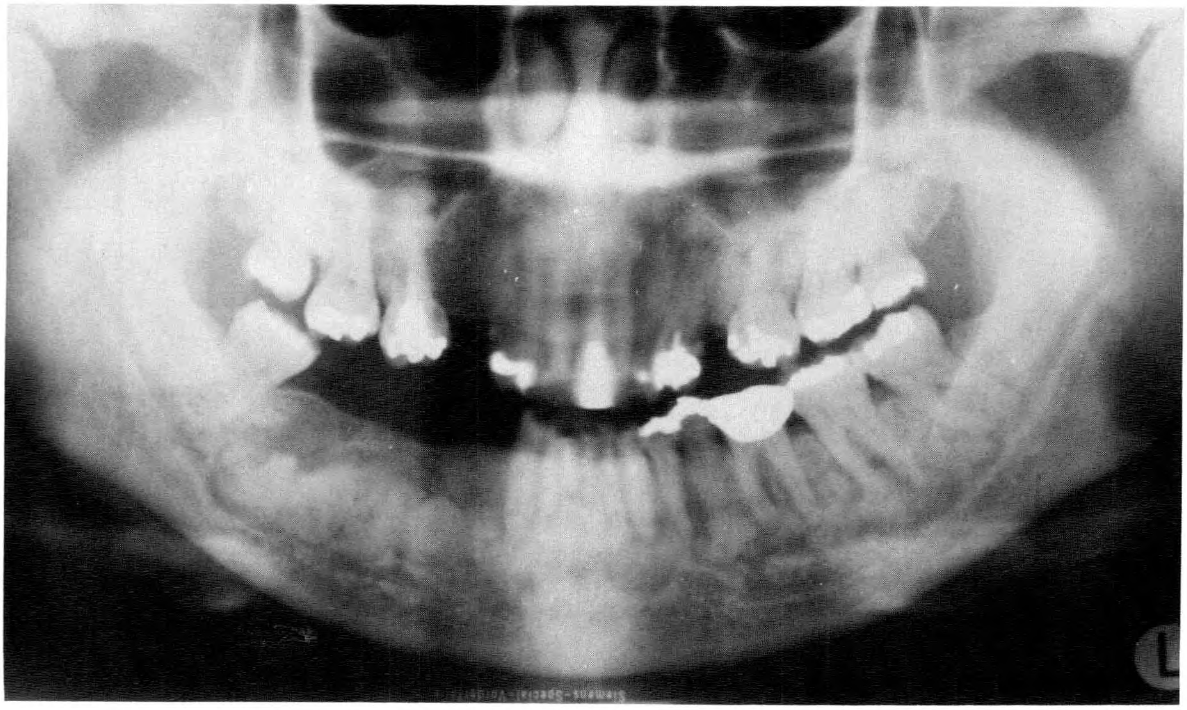

FIG. 1.

Orthopantomogram showing multiple lobulated radiopaque masses present in both the mandible and the maxilla.

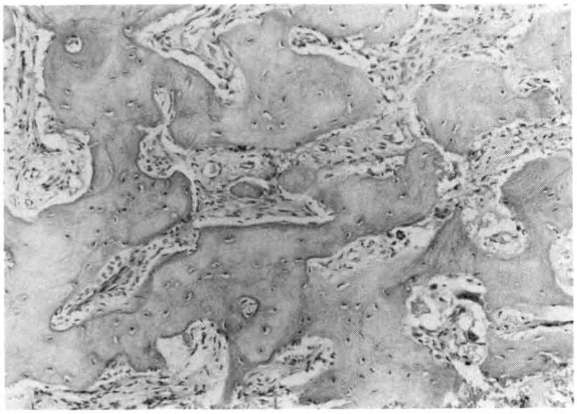

FIG. 2.

Photomicrograph (magnification × 120) showing relatively acellular areas of fusion of calcified material within a fibrous stroma.

This revealed multiple lobulated radiopaque masses with radiolucent peripheries symmetrically distributed throughout both the maxilla and the mandible (Fig. 1). The appearance resembled a gigantiform cementoma, but other conditions such as osteopetrosis, chronic diffuse sclerosing osteomyelitis, cementifying fibroma, and Paget's disease could not be excluded. Further investigations revealed a normal haemoglobin and differential white cell count but a raised erythrocyte sedimentation rate of 25 mm/h, probably due to the patient's sarcoidosis. The serum calcium, phosphorus, alkaline phosphatase and albumin were within normal limits. The patient did not exhibit sensory loss in the distribution of the inferior dental nerves.

In view of the expansion of the right body of the mandible, the sclerotic mass was removed under endotracheal anaesthesia, and the specimen sent for histopathological examination. The lesional tissue was reported as being relatively acellular, basophilic, calcified materal, within a fibrous stroma, showing areas of fusion (Fig. 2), the appearances being consistent with a gigantiform cementoma.

DISCUSSION

Cases with characteristics similar to the gigantiform cementoma have been reported in the past as sclerosing osteitis, chronic productive osteitis, osseous dysplasia and multiple bony exostosis (Shafer, 1957; Laband and Leacock, 1967; Bhaskar and Cutright, 1968; Waldron et al, 1975).

It seems, therefore, a possibility that some of these cases may have been misdiagnosed. A firm diagnosis of gigantiform cementoma cannot be made on radiological evidence alone; Paget's disease, which may have radiological similarities, shows biochemical differences and must be excluded because of the possibility of sarcomatous change (Karpawich, 1958; Rosenmertz and Schare, 1969). The gigantiform cementoma is essentially a benign condition (Winer et al, 1972). Studies by Zegarelli et al (1964) were unable to link the condition to any specific disease or drug therapy, and it seems unlikely that this patient's sarcoid therapy can be related.

It has been suggested that lesions which are asymptomatic and quiescent should be left untreated (Waldron, 1975). Surgery becomes necessary when the lesion expands and causes facial deformity, as in our case, or when the lesion becomes infected. The deposition of cementum impairs the vascularity of the bone and is said to predispose the bone to infection (Van der Waal & Van der Kwast, 1974). Radiological review of these lesions at yearly intervals is recommended.

The object of this paper is to report a case of gigantiform cementoma which presented as an alarming radiological incidental finding. The increased use of the orthopantomogram, especially in regions of high negroid populations, may show that this condition is more common than previously suspected. It is a benign condition, and in most instances treatment is conservative.

ACKNOWLEDGMENTS

We wish to thank Mr D. Henderson, Consultant Oral and Maxillofacial Surgeon, St Thomas' Hospital, London, for allowing us to report this case, and Mr Khee Whee Lee, Senior Lecturer in Oral Pathology at the Eastman Dental Hospital, London, for his help and assistance with this paper.

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Duodenal haematoma mimicking traumatic pancreatic pseudocyst

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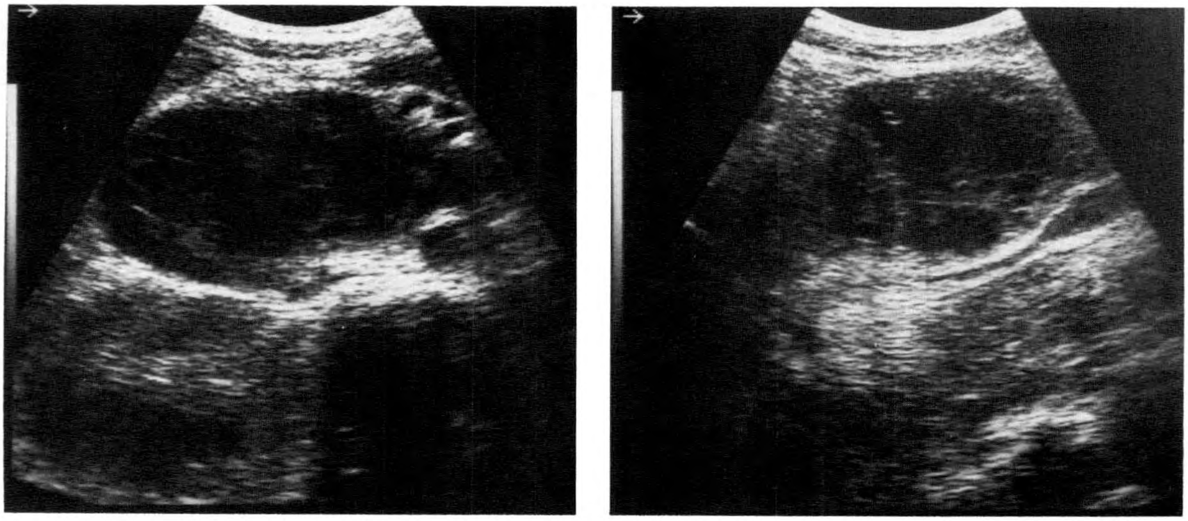
Duodenal haematoma and pancreatic pseudocyst are both rare but well recognised complications of blunt abdominal trauma. We present a case where clinically, biochemically and radiologically, duodenal haematoma mimicked the findings normally associated with pancreatic pseudocyst.

CASE REPORT

An 11-year-old boy was admitted via the Casualty Department of this hospital with a 3-day history of abdominal pain and bile-stained vomit. This followed a fall in the school gymnasium where he had been struck in the abdomen by the end of a school bench. On examination the main findings were of central abdominal tenderness with an ill-defined central abdominal mass. Haematological examination was normal. Biochemical assessment showed evidence of mild dehydration and a serum amylase of 4800 Smogyi units. A plain abdominal radiograph confirmed the presence of a mass in the epigastric region.

An ultrasound examination was performed 12 h after admission. This showed a large cystic mass with centrally contained echoes, lying in the region of the head of the pancreas, which was thought to represent a traumatic pancreatic pseudocyst.

A repeat scan 48 h later showed the cystic mass to have increased in size to 10 cm (Fig. 1). In addition, it was noted that the gallbladder was markedly enlarged and contained echogenic bile. The common bile-duct was dilated at 1 cm (Fig. 2). The spleen was also enlarged and the splenic vein was seen to be dilated and tortuous in the splenic hilum. The findings seemed to confirm the presence of a pancreatic pseudocyst. However, the typical dependent debris often present within a pseudocyst was not seen, and within the cyst numerous mobile strands were seen, suggesting the presence of fibrin formation, therefore raising the possibility of a



A B

FIG. 1.

(A) Transverse scan in the upper abdomen showing a cystic mass. The strands it contains were seen to be mobile on real-time scanning. (B) Longitudinal scan of same region.

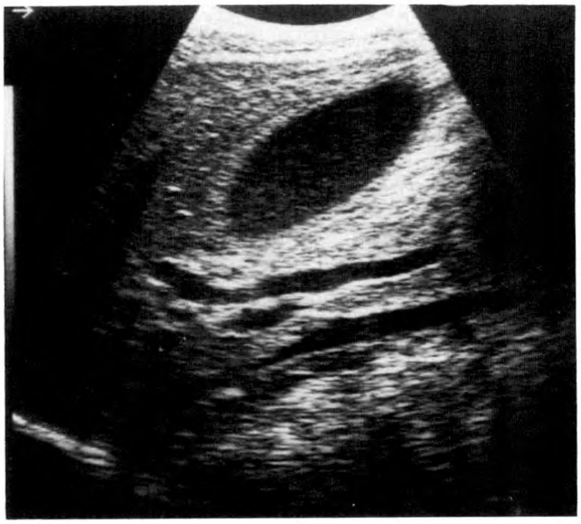


FIG. 2.
Scan through gallbladder showing echogenic bile-filled gallbladder and dilated common bile-duct.

haematoma. A barium meal study was performed. This showed the classical changes of a duodenal haematoma (Fig. 3) with almost complete obstruction of the duodenum.

The child was managed conservatively and made a full recovery. Serial scans have shown resolution of the haematoma. The gallbladder, common bile-duct, spleen and splenic vein have all returned to normal dimensions. A subsequent barium meal study has shown an essentially normal duodenum.

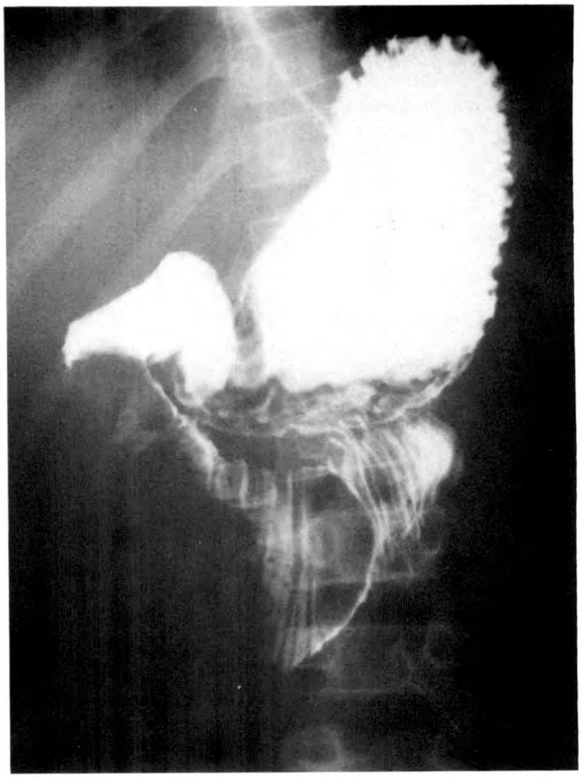


FIG. 3.
Barium study showing an intramural mass displacing duodenal loop cranially and medially.

DISCUSSION

Duodenal haematoma and pancreatic pseudocyst are uncommon complications of blunt abdominal trauma in children, with a reported incidence each of the order of 1–2% (Graham et al, 1978; Kaufman et al, 1984).

This case illustrates how difficult it may be to distinguish between these two conditions. The correct diagnosis has important clinical implications; duodenal haematoma is generally managed conservatively, whereas a pancreatic pseudocyst may require surgical drainage.

The history and clinical examination can only suggest the differential diagnosis. The serum amylase may be a helpful pointer to pancreatic damage but, as this case shows, a duodenal haematoma may obstruct the ampulla of Vater, the resulting pancreatic duct stasis producing a rise in serum amylase. The amylase, even at the very high levels which occurred in this case, is not specific for pancreatic trauma (Olsen, 1973; Moretz et al, 1975).

Ultrasound demonstration of a dilated common bile-duct and biliary stasis has been reported with pancreatic pseudocyst and duodenal haematoma (Foley and Teele, 1979). The mechanism for this is as outlined above. Similarly, obstruction of the splenic vein, although to our knowledge not previously reported, can theoretically be caused by either lesion, and does not serve to distinguish between the two.

The most discriminating examination is the barium meal. The features of duodenal haematoma on barium meal were first reported in 1954 (Felson & Levin, 1954). This case exhibits the features as described then, with a sharply marginated intramural mass which widened the lumen of the duodenum, and a "coiled spring" appearance.

In this situation a barium meal study served to distinguish between duodenal haematoma and pancreatic pseudocyst, since with the former the duodenum is displaced medially and cranially, whereas in the latter one would expect to see a widened duodenal loop displaced laterally and caudally.

In summary, following blunt abdominal trauma, distinction between duodenal haematoma and pancreatic pseudocyst can be very difficult. When clinical and biochemical examinations and ultrasound scanning suggest these as likely diagnoses, then a barium meal study may quickly and simply lead to the correct diagnosis.

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Takayasu's arteritis: decrease in aortic wall thickening following steroid therapy, documented by CT

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Takayasu's arteritis is a well-known disease entity which most frequently affects the thoracic aorta and its branches. The wall of the aorta is thickened, and the degree of thickening may change during the course of the disease.

Steroids are effective in treating the inflammatory process of the arteritis. The effect is usually manifested by improvements in laboratory data and symptoms. This is a report of an acute case of Takayasu's arteritis in which considerable decrease in aortic wall thickening followed steroid therapy is documented by computed tomography (CT).

CASE REPORT

A 17-year-old girl was admitted with a history of intermittent nasal bleeding and headaches of several years' duration, and recently-detected systolic hypertension as high as 250 mm Hg. Laboratory findings on admission included an elevated erythrocyte sedimentation rate (114 mm h^{-1}), and a C-reactive protein of + + +. Her blood pressure was 186/70 mm Hg in the upper extremities, and 84 mm Hg systolic in the lower extremities. Retinoscopy was normal.

Chest radiography revealed minimal cardiomegaly and notching of several ribs (Fig. 1). Coarctation of the aorta and Takayasu's arteritis were suspected. An initial CT scan performed on May 31, 1983 disclosed marked thickening of the aortic wall (probably associated with periaortic infiltration) (Fig. 2). Thoracic aortography demonstrated marked narrowing of the descending aorta at two sites, and marked thickening of the aortic wall (Fig. 3).

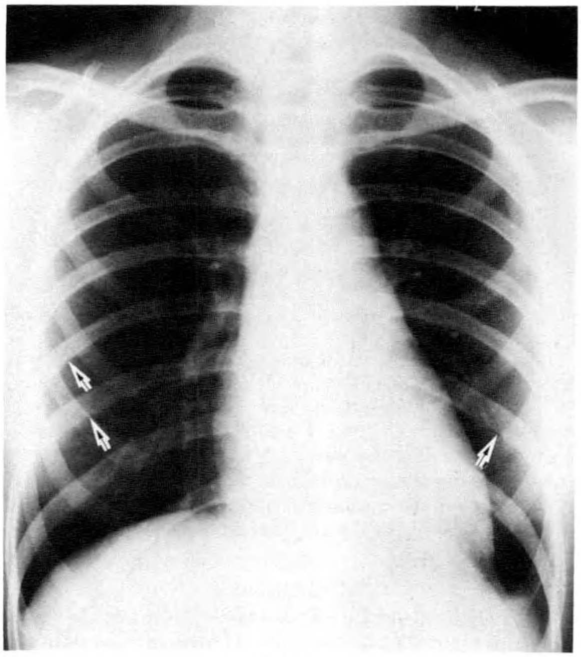

FIG. 1.

Admission chest radiograph shows minimal cardiomegaly and notching of several ribs (arrows). Prominence of the aortic arch and poor definition of the lateral border of the descending aorta are also observed.

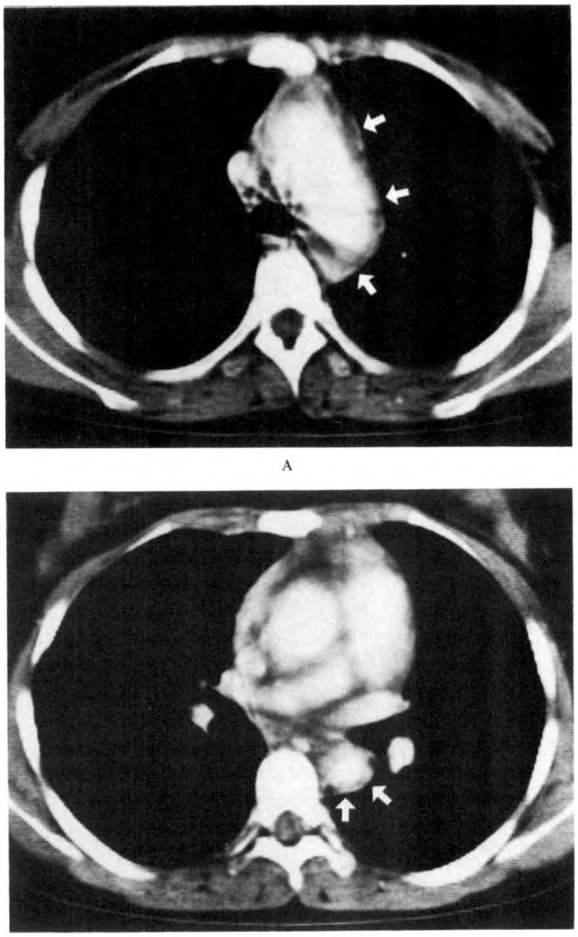

FIG. 2.

Initial CT scan (May 31, 1983), at the level of aortic arch (A) and the descending aorta (B) shows marked thickening of the aortic wall.

Takayasu's arteritis was diagnosed, and steroid therapy was begun on June 11, 1983 (Prednisolone 30 mg/day for ten days, and 20 mg/day thereafter). Her laboratory data rapidly improved. On July 19, 1983, the ESR was 18 mm h^{-1}, and C-reactive protein was negative.

A follow-up CT scan on January 12, 1984 showed reduction in the degree of aortic wall thickening (Fig. 4). Blood pressure in her upper extremities has remained elevated.

DISCUSSION

Takayasu's arteritis (Takayasu, 1908) occurs most frequently among young oriental women, though the disorder has been observed worldwide. It most often affects the thoracic aorta and its branches, and also the pulmonary arteries. Stenosis and obstruction are characteristic although dilatation and aneurysms are not rare (Hachiya, 1970; Lande & Berkmen, 1976).

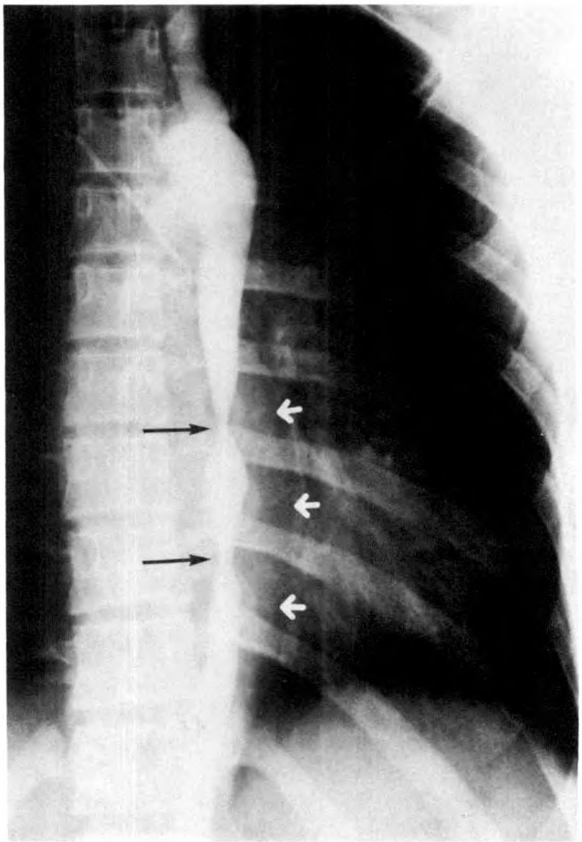

FIG. 3.

Thoracic aortogram demonstrates two sites of marked stenosis in the descending aorta (black arrows). The wall of the descending aorta is markedly thickened. Its lateral border is rather poorly defined (white arrows).

The pathological findings in this condition have been well described by Nasu (1963, 1975). Arterial lesions are histologically classified as granulomatous inflammation, diffuse productive inflammation and fibrosis. Inflammatory changes are most severe in the media, and less so in the adventitia. Occasionally, perivascular infiltration by a variety of cells occurs around the vasa vasorum, and the infiltrate may extend to adjacent adipose tissue. Intimal changes are said to be secondary to those in the media and adventitia.

In living subjects the thickness of the thoracic aortic wall has been measured as the distance between the intraluminal contrast medium and the air in the lung on the aortograms. This distance includes not only the thickness of the aortic wall itself, but that of the two layers of the pleura (the latter should be negligible), and possibly periaortic infiltration as well. With the development of CT, it was hoped that the thickness could be measured noninvasively, but this is not always possible because of the limited spatial resolution of CT

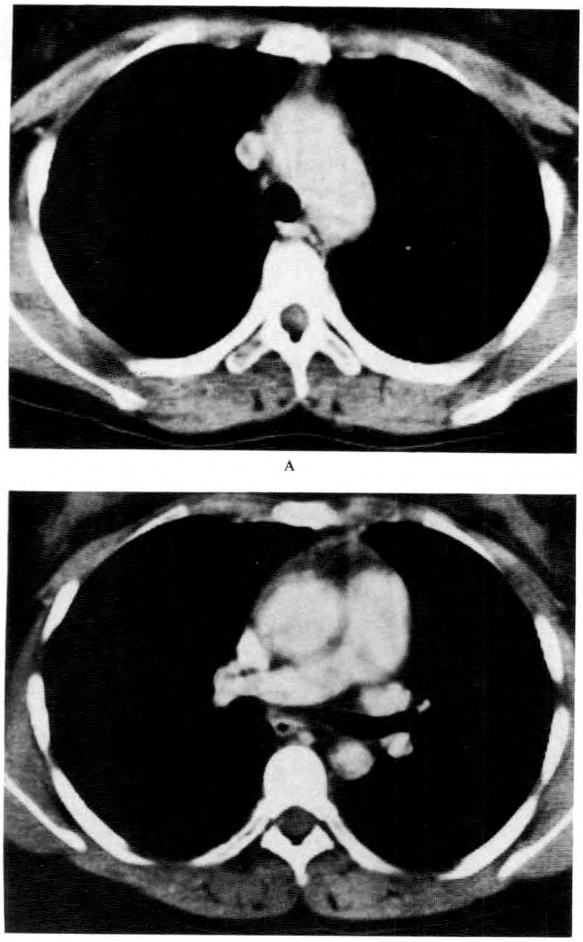

FIG. 4.

Follow-up CT (January 12, 1984) at the level of the aortic arch (A) and the descending aorta (B) shows marked reduction of the thickening of the aortic wall (more apparent around the arch).

and the marked change in calibre of the aorta during the cardiac cycle. Considerable thickening, however, may be demonstrated by CT as in the present case. It should again be noted that the thickening may be partly or largely due to periaortic infiltration.

During the course of Takayasu's arteritis, either spontaneously or with steroid therapy, the aortic wall thickening may be reduced, corresponding to the decrease in the active inflammation in and around the aortic wall. This is the first report of a case of Takayasu's arteritis in which reduction of the aortic wall thickening following steroid therapy was documented by CT scans. Tamaki et al (1976) have observed the same phenomenon on conventional chest radiography.

Another radiographic finding of interest is the loss of sharp definition of the descending thoracic aorta, as observed on the conventional radiograph and on the aortogram (Figs. 1,3). The "filling in" of the concavity between the heart and the descending aorta by perivascular infiltration may be the cause of this phenomenon (Tamaki et al, 1976).

The manifestations of Takayasu's arteritis on chest radiography include cardiac enlargement, pulmonary oligaemia, rib notching, segmental or generalised aortic dilatation, aortic calcification, and a wavy or scalloped appearance of the descending aorta (Iinuma, 1961; Gillanders & Strachan, 1965; Hachiya, 1970; Berkmen & Lande, 1975). Loss of the sharp definition of the descending aorta may be added to these manifestations.

ACKNOWLEDGMENTS

We thank Dr. Walter J. Russell of Radiation Effects Research Foundation for reviewing this manuscript. We also thank Mr. Yoshihiro Hayashida, Ms. Terumi Kanaya, Ikuko Uematsu and Mutsumi Noguchi for their help in preparing this manuscript.

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Case reports

Unusual ultrasound appearance of the spleen—a case of hereditary spherocytosis

By Renu Gupta, M.D. and *C. H. Woodham, F.R.C.R.

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(*Received August 1985*)

A case of hereditary spherocytosis having an unusual appearance on ultrasound of the spleen due to histologically proven extramedullary haematopoiesis in the spleen is presented.

CASE REPORT

A 66-year-old man was admitted to hospital for right upper quadrant pain radiating to the back. He was jaundiced and his abdomen was tender with guarding. Murphy's sign was positive. The spleen was palpable 2 cm below the left costal margin. His routine blood film showed a picture of hereditary spherocytosis. An abdominal ultrasound was performed which revealed focal areas of very high echogenicity within an enlarged spleen, having well defined outline, resembling metastatic deposits (Fig. 1). The patient underwent laparotomy, cholecystectomy and exploration of common bile-duct. Splenectomy was performed in view of his hereditary spherocytosis. He made a good post-operative recovery. A cut section of the spleen revealed several well circumscribed areas of softening (Fig. 2) corresponding in position and size to the focal areas of increased echogenicity seen on ultrasound. The histopathology report stated, "soft areas are composed of grossly dilated sinuses and even more prominent extra-medullary haematopoiesis. The appearances look as though this area of spleen is trying to turn itself into bone marrow" (Fig. 3). The gallbladder showed changes of chronic cholecystitis, but no calculi were found.

DISCUSSION

Hereditary spherocytosis is an autosomal dominant disorder occurring in one in 4500 of the population. Compensatory normoblastic hyperplasia of bone marrow occurs with extension of red marrow into the midshaft of long bones, and occasionally with extra-medullary haematopoiesis leading to formation of paravertebral masses visible on chest radiographs.

The spleen usually enlarges in hereditary spherocytosis and ultrasound appearances of the spleen have been described in two such cases (Mittelstaedt & Partain, 1980; Silver et al, 1980; Mittelstaedt, 1981). In both cases, the spleen showed homogeneous increased echogenicity, in contrast to the appearances in our case.

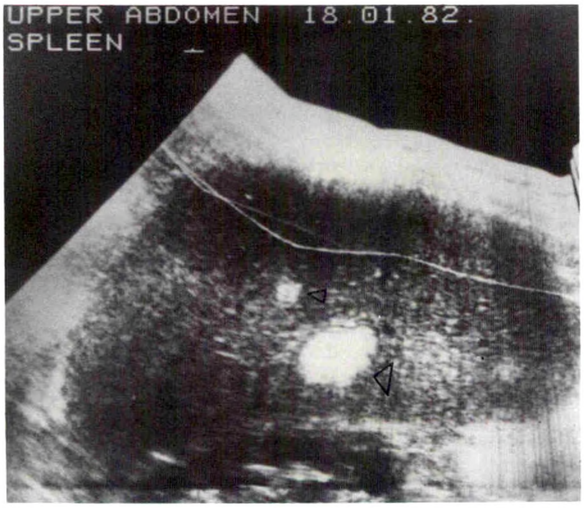

FIG. 1.

Ultrasound scan showing well defined focal defects of high echogenicity relative to normal spleen (arrows).

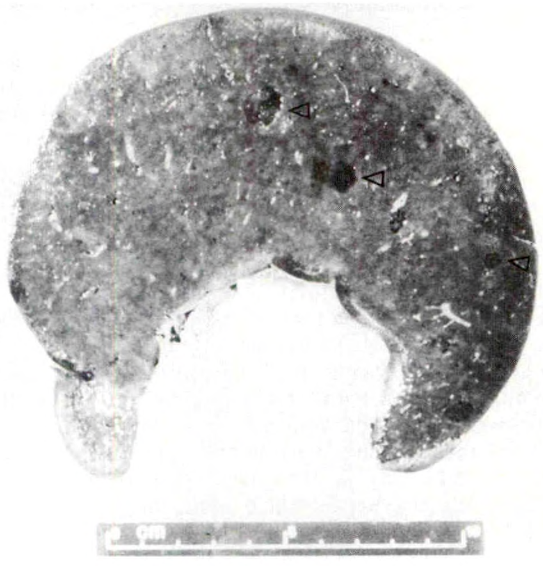

FIG. 2.

Cut section of spleen showing well circumscribed areas of softening (arrows).

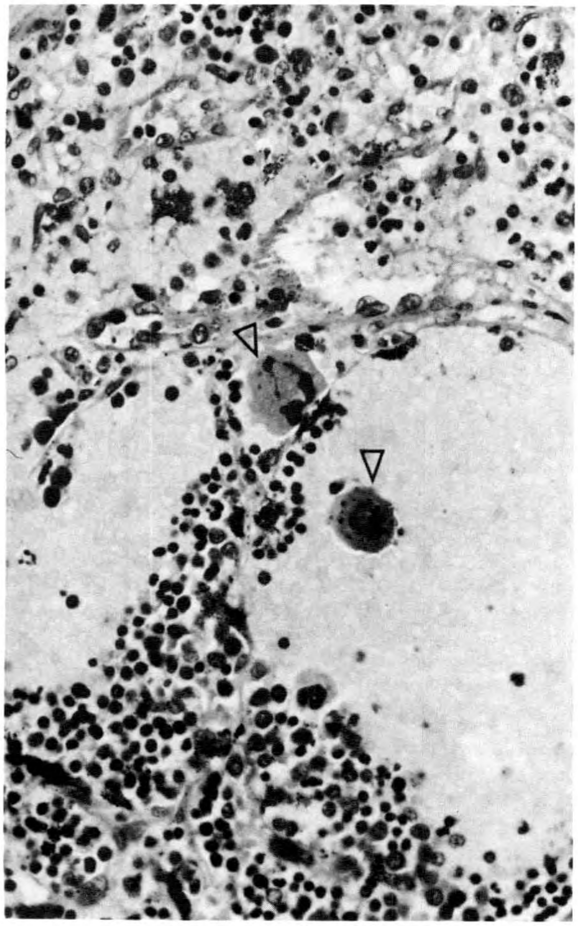

FIG. 3.

High power photomicrograph of area of softening to show extramedullary haematopoiesis. Megakaryocytes (arrows) are numerous and surrounded by other cells in the erythroid and granulocytic series. H and E, × 500.

Ultrasound appearances of focal lesions of the spleen have been described in cysts, abscesses, lymphomas, metastases, haematomas, infarcts, haemangiomas and benign neoplasms (De Graaff et al, 1979; Solbiati et al, 1982; Costello et al, 1985). Our case showed histologically proven focal areas of extramedullary haematopoiesis corresponding to the ultrasound appearance of the spleen. To our knowledge, such an appearance has not been described before.

ACKNOWLEDGMENT

Renu Gupta wishes to thank the Siemens Foundation for a Scholarship to the University Department of Radiology, University of Oxford.

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Book reviews

Atlas of Roentgenographic Measurement, 5th edit. By Theodore E. Keats and Lee B. Lusted, pp. 450, 1985 (Year Book Medical Publishers, Inc., Chicago), £55 00
ISBN 0-8151-5656-1

In preparing the 5th edition of this standard work, the authors have had to contend with the enormous amount of routine measurements which have become associated with ultrasound, computed tomography, and other modalities over the 7 years since the previous edition. To do this, without making the book too massive, a large number of previous entries have been omitted "either because they have not proved useful in everyday practice, or because they have been replaced with new material. The new entries have been selected for their usefulness in clinical practice, their ease of application and for their validity".

The authors are to be congratulated in keeping the book to a manageable size—indeed, on superficial examination it looks no different in size from the previous edition. However, the nature of the material does not demand the usual radiographic quality necessary in standard textbooks. Since most of the illustrations are tables, graphs, or charts, it has been possible to use paper which keeps the volume similar to previous editions.

I suspect that many British radiologists are less statistically minded than their transatlantic counterparts, and are sceptical about drawing lines on radiographs and taking measurements, fearing that this takes away the art of recognising the normal and abnormal, and reduces medicine to a mere science. The authors forestall this and similar criticisms by stating in their preface that they have always eschewed the word "normal", and that they usually present the measurements for a definite population in terms of mean and standard deviation, although percentiles may be used. Some of the tables are rather esoteric: I wonder how many of us would regularly refer to the tables measuring the "relationship of the stomach and duodenum to the spine in different weight and stomach type groups." Some of the topics, however, are time-honoured and are of everyday use, *e.g.* the normal range of spinal canal diameters, metacarpal index etc , but we are now given, in addition, such measurements as the range of size and number of all lymph nodes in the upper tracheal retrocaval space on CT. Unfortunately this is one field where the quality of reproduction does suffer, and the interested reader would probably need to refer to the original article in some of the CT references (the quality of ultrasound reproduction is predictably better). Anatomical measurements for head and body CT are included, but tissue density measurements, "do not yet seem to be well enough standardised in most instances "

With an old friend like this, packed full of proven and valuable facts, the book sells itself on its own merit and reputation At least one copy is essential in every department, as unfortunately they quickly disappear into the hands of private collectors. To young radiologists, who have not met it before, I would say: Go and buy your own copy–you won't regret it, but never let it out of your sight!

J. T. PATTON

Encyclopedia of Medical Radiology, Vol. 20. Radiation Exposure and Radiation Protection By F. Heuck and E. Scherer, pp. xxv+730+index, 1985 (Springer Verlag, Berlin), DM. 880.
ISBN 3-540-13155-8

This book, written in German, gives a comprehensive description of the effects of excessive radiation and how these can be modified by anoxia and other chemical means. These descriptions will be of greater interest to radiotherapists and to students of the atom bomb, industrial accidents and cellular biology than to diagnostic radiologists, who are concerned with much lower radiation doses. There then follow detailed descriptions of the effects of radiation on all the body systems in turn. There is a section on occupational exposure and dose limits Means of reducing radiation dosage by means of good technique are not discussed, nor are methods of measuring radiation.

The editors have not managed to introduce uniformity into the units of measurement, so that both old units and SI units are discussed. The index is excellent and includes references from 1984 Unfortunately for the authors, the NRPB have just issued a new code of practice. Apart from this the book will be a valuable source of reference to anybody interested in the effects of radiation on human tissues or planning to lecture on this subject

G. M STEINER

1986, *The British Journal of Radiology*, *59*, 287–288

MARCH 1986

Case of the month

The case of the missing sign

By G. Wagener, M.B., Ch.B., B.Sc., M. Sandler, M.B., Ch.B., M.R.C.P. and F. S. Hough, M.D.

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(*Received March 1984*)

A 51-year-old female presented with a 6-month history of malaise and recent onset of left renal colic. An excretory urogram demonstrated a ureteric calculus, which was removed and found to be predominantly of calcium content.

Biochemical investigations revealed a raised total serum calcium of 2.8 mmol/l (normal = 2.1–2.6* mmol/l), low to normal serum phosphate of 0.79 mmol/l (normal = 0.8–1.4 mmol/l), and a persistently raised total serum alkaline phosphatase of 120–130 IU/l (normal = 30–100 IU/l). Renal function was normal.

A skeletal survey showed vertebral biconcavity with increased vertical striations, indicating axial osteopenia. An orthopantomogram of the mandible demonstrated absence of teeth and multiple medullary cystic lesions with thinning of the cortex (Fig. 1).

Fine-detail radiographs of the hands were made and examined, by means of a 6-power magnifier with a built-in 0.1 mm scale, to measure cortical widths and to detect cortical erosions. The Exton-Smith metacarpal index of cortical area (Exton-Smith et al, 1969) was markedly lowered below the 10th percentile for the patient's age and sex. This indicated osteopenia. No subperiosteal phalangeal bone resorption could be seen (Fig. 2).

The rest of the skeleton was radiologically normal.

What is your provisional diagnosis and what other investigations would be helpful?

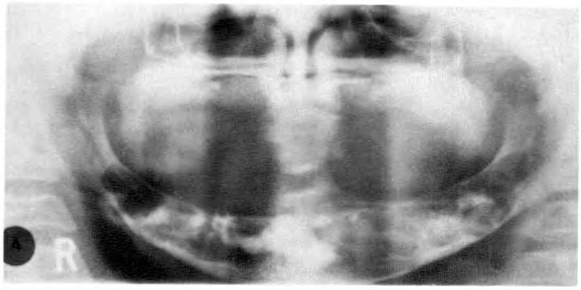

FIG. 1.

An orthopantomogram showing multiple cysts in the mandible with thinning, but not destruction, of the cortex. No comment could be made on lack of lamina dura as the patient was edentulous.

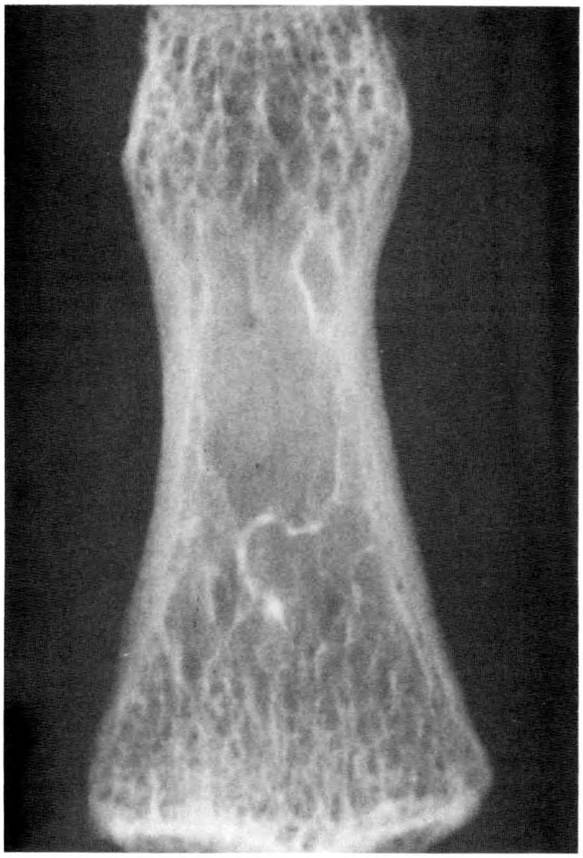

FIG. 2.

Fine-detail radiograph of a phalanx of the hand showing no subperiosteal resorption. × 6.

Address for reprints: Dr G. W. W. Wagener, Department of Radiology, Tygerberg Hospital, Tygerberg 7505, Republic of South Africa.

*Normal values used in Tygerberg Hospital.

FURTHER INVESTIGATIONS AND TREATMENT

Plasma parathyroid hormone, measured by C-terminal radioimmunoassay, was significantly increased and ranged from 290–320 pmol/l (normal = 0–130 pmol/l).

Biopsy of the cystic lesions in the jaw showed localised collections of fibrous tissue and giant cells, in keeping with the histological diagnoses of "brown tumours". Neck exploration was performed during which four hyperplastic parathyroid glands were removed.

Osteitis fibrosa cystica refers to the bony changes seen in hyperparathyroidism. This condition is characterised radiologically by the presence of osteopenia, subperiosteal resorption of cortical bone and the development of brown tumours, which are localised accumulations of giant cells and fibrous tissue. The brown tumours are frequently found in the jaw or facial bones, but may present in any part of the skeleton. However, the occurrence of brown tumours in the absence of phalangeal subperiosteal resorption in the hands is rarely encountered (Steinbach et al, 1961). Two such cases have been reported (Pugh, 1961), but in both cases only standard radiographs of the hands were done. Fine-detail magnification radiography of the phalanges is important for the early diagnosis of subperiosteal erosions. It has a diagnostic accuracy of 50–60%, in comparison to 0–29% for ordinary hand radiographs in different series (Genant et al, 1973; Weiss, 1974).

Osteopenia, as part of or as the presenting feature of hyperparathyroid bone disease, has repeatedly been described. By measuring the metacarpal cortical index, osteopenia could be detected in 86% of 162 cases with primary hyperparathyroidism (Gryfe, 1973). It is thus likely that osteopenia is an earlier, although non-specific, sign of primary hyperparathyroidism than subperiosteal resorption.

Our patient with primary hyperparathyroidism was unusual in that she had brown tumours, a sign of advanced osteitis fibrosa cystica, without any evidence of phalangeal subperiosteal resorption, which is usually an early feature of hyperparathyroid bone involvement.

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1986, *The British Journal of Radiology*, 59, 289–292

MARCH 1986

Short communications

Three-dimensional anatomical images from computed tomographic scans

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(*Received June 1985 and in revised form August 1985*)

A standard computed tomographic (CT) examination provides the observer with a series of cross-sectional images through an area of clinical interest. These images are based on digital information which can then be reformatted in the coronal, sagittal or oblique plane. Both cross-sectional and reformatted CT images are two-dimensional, however, requiring a process of mental integration of multiple sections to be performed by the observer in order to derive three-dimensional information.

In areas of complex anatomy it can be difficult even for a skilled radiologist experienced in CT to perceive the third dimension from standard CT sections. Moreover, when reconstructive surgery is planned in such areas, a surgeon may be unable to extract easily the precise anatomical and volumetric detail he requires from conventional CT sections alone.

To overcome this problem, computer software has been developed (Marsh & Vannier, 1983a; Udupa, 1983) to enable three-dimensional (3D) images to be produced from a series of standard CT slices. Initial reports suggested that clinically useful images could be created using such programs, particularly in cases of skeletal trauma and craniofacial deformities (Hemmy et al, 1983; Marsh & Vannier, 1983b, Totty & Vannier, 1984). Vannier et al (1984) have reported several illustrative cases representative of their experience in craniofacial deformities in over 300 patients, showing the value of their own 3D computer methods. More recently Burk et al (1985) have described their experience of 3D images in 20 patients with acetubular fractures.

In this preliminary report we present our early experience of 3D images generated by a new program entitled "3D83", and discuss the potential advantages of the technique.

METHOD

All investigations have been carried out in the Department of Diagnostic Radiology, University of Manchester, using an IGE CT/T 8800 scanner. The input to the 3D83 program developed by the Medical Imaging Processing Group at the University of Pennsylvania for General Electric Medical Systems is a series of conventional CT slices. For optimum anatomical detail contiguous 1.5 mm sections (120 kVp, 400 mA, PWC 2, 576 views) were obtained, though 5 mm sections (120 kVp, 320 mA, PWC 2, 342 views) were used for large volumes of tissue such as the pelvis. Intravenous contrast enhancement was employed only when vascular structures, blood vessels and intracranial tumours were investigated. Both patient movement and streak artefacts due to metal resulted in degradation of the reconstructed 3D image, and were avoided whenever possible.

The picture elements (pixels) that form the substrate for the 3D reconstruction were selected from each CT slice using the "Measure" or "Identify" pixel display facility on an IGE independent physician's display console (IPDC). Using the "Measure" mode, the pixel theshold level was adjusted until the required tissues were displayed. A threshold level of 150 Hounsfield Units, for example, would include only bone, while levels below this would incorporate bone plus varying amounts of soft tissue. A region of interest (ROI) was then designated which enabled only the relevant areas of the input CT sections to be included in the 3D reconstructions. Thus the facial bones could be displayed without the adjacent cranium.

After processing on a Data General Eclipse S/140 computer the reconstructed volume was usually viewed as a series of single images as if obtained at varying increments during a 360° rotation around multiple axes, up to a maximum of 60 images per axis or rotation. As an alternative, the reconstructed volume was viewed continuously rotating in "cine mode" using the GEDIS (General Electric Medical Systems) research package.

The grey scale was used to denote depth rather than tissue density, points closer to the observer thus appearing brighter than those further away.

ILLUSTRATIVE CASES

Case 1

A 33-year-old man received a blow to the left cheek with a blunt instrument. A vertical fracture line can be seen running up the left maxilla and lateral wall of the left orbit, together with a comminuted left antral fracture and fronto-zygomatic suture separation (Fig. 1A, B) Soft-tissue swelling is also evident (Fig. 1C).

Case 2

A 35-year-old man presented with vertigo and right-sided deafness. A large right-sided acoustic neuroma was identified on CT scans performed during intravenous contrast infusion. The relationship of the tumour to intracranial bony landmarks is well shown in Fig 2.

Case 3

A 22-year-old man sustained a head and neck injury at work. Plain radiographs and tomograms demonstrated a possible fracture of C1. CT examination excluded any bony injury. Rotational malalignment between C1 and C2 due to soft-tissue injury was more easily appreciated on the 3D image (Fig. 3).

Case 4

A 17-year-old man with a cleft palate deformity underwent CT examination prior to surgical correction. This also revealed multiple congenital anomalies at C1 and C2 due to non-fusion of the three ossification centres of the odontoid process

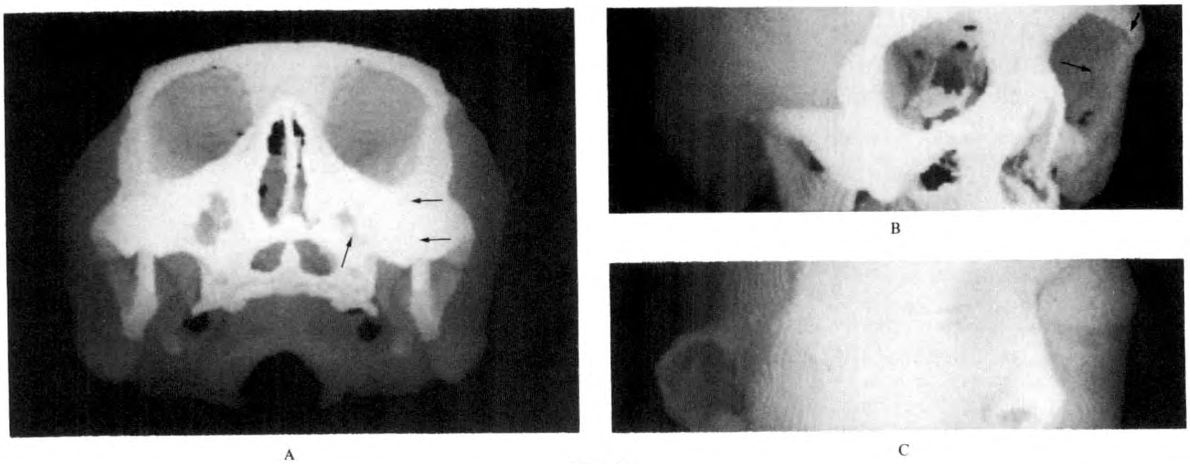

FIG. 1.

Fractures of the left maxilla and antrum (arrows) extending up the lateral wall of the left orbit (long arrow) with disruption of the fronto-zygomatic suture (short arrow). The defect in the right maxilla is artefactual due to thin bone. (A) Antero-inferior view. (B) Lateral oblique view. (C) Soft tissue view in same orientation as (B), demonstrating swelling at the site of injury.

(Fig. 4A, B). The odontoid base is represented by two divergent columns with a third segment lying adjacent to the skull base. A small anterior spina bifida defect is also present in C1.

Case 5

An elderly man with Paget's disease of the pelvis fell and sustained a pathological fracture through the right iliac wing. The malalignment on healing is well demonstrated in Fig. 5.

Case 6

A prosthetic left hip joint in a 59-year-old man became infected and was subsequently removed. The resulting abnormal left hip is shown in Fig. 6A. Absence of a femoral head made it possible to display the left hemi-pelvis without the femur and to demonstrate a defect in the medial acetabular wall (Fig. 6B). Conversely, the abnormal femur could be displayed without the left hemi-pelvis (Fig. 6C).

DISCUSSION

The anatomical surfaces best suited to reconstruction by the 3D program are those immediately adjacent to areas or volumes of markedly different attenuation. Bone and external soft-tissue outlines are therefore ideal. The use of intravenous contrast medium allows vascular structures and enhancing intracranial tumours to be differentiated from surrounding soft tissue in the reconstruction.

An important aspect of 3D images is their digital origin, which enables a variety of image processing techniques to be

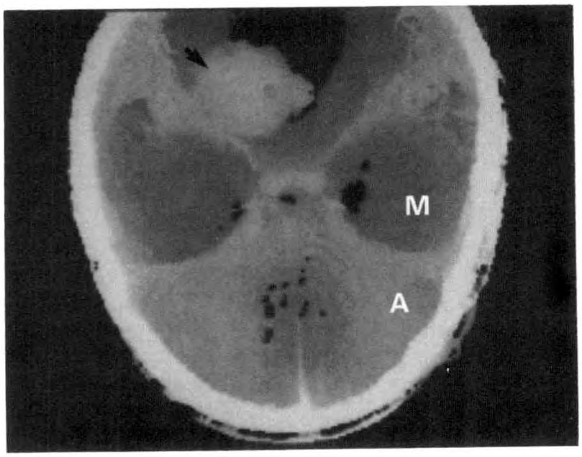

FIG. 2.

Superior view of the skull floor showing a large acoustic neuroma in the right posterior fossa (arrow). M, middle cranial fossa; A, anterior cranial fossa.

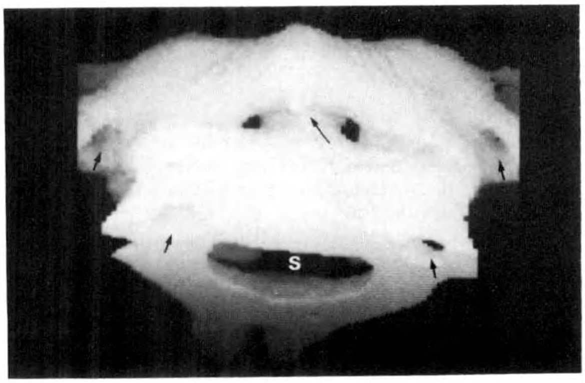

FIG. 3.

Antero-inferior view of C1 and C2 showing rotational malalignment between the vertebrae. The odontoid process can be traced upwards until it passes behind the anterior arch of C1 (long arrow). Transverse foramina (short arrows) and the spinal canal (S) are indicated.

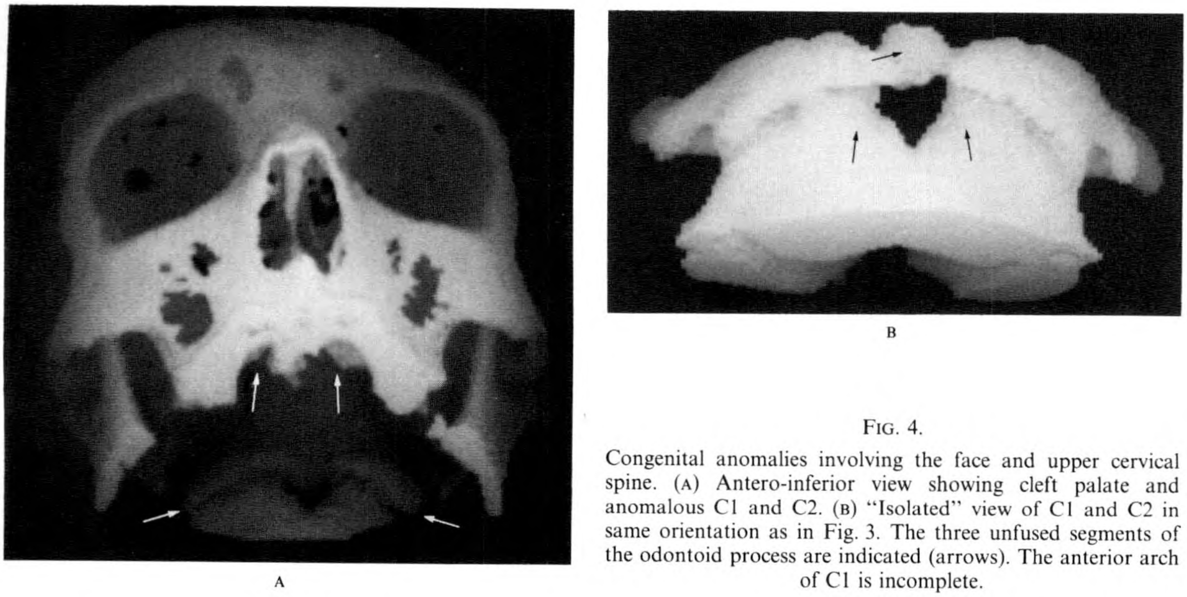

FIG. 4.

Congenital anomalies involving the face and upper cervical spine. (A) Antero-inferior view showing cleft palate and anomalous C1 and C2. (B) "Isolated" view of C1 and C2 in same orientation as in Fig. 3. The three unfused segments of the odontoid process are indicated (arrows). The anterior arch of C1 is incomplete.

employed. Areas of clinical interest can be "isolated" from the patient and viewed in a variety of orientations not possible using other methods. Distances between any spatial co-ordinates can be measured with precision. A cranio-caudal view, for example, permits intervertebral rotation to be measured (Case 3).

Anatomical information is displayed without superimposition of other structures and in a more familiar format than conventional CT cross-sections. In complex anatomical regions such as the facial bones, 3D images can make interpretation of an otherwise difficult set of cross-sectional CT images easier and less time-consuming for both radiologist and referring clinician. The potential for planning surgical reconstructive procedures and post-operative evaluation is self-evident.

Total CT scanning time for a facial or pelvic examination is about 45 to 60 minutes. The computing time for a series of 3D images on one patient can vary from under one hour to several hours. This time is determined by several factors, including the number of axes of rotation, the number of frames per rotation, and the size of the volume to be reconstructed. The computer can, however, be programmed to perform the reconstructions overnight, making use of what might otherwise be "downtime".

Radiation dose and slice profile measurement performed on our IGE CT/T 8800 scanner have shown that with commercially available collimation any increase in radiation dose associated with the reduction of CT slice width is proportional only to the change in mAs required to maintain image quality. In our department the use of 1.5 mm rather than 10 mm sections for head examinations requires a 25% increase in mAs from 491 to 614. In the pelvis, reduction in slice width from 10 mm to 5 mm does not normally require any change in mAs.

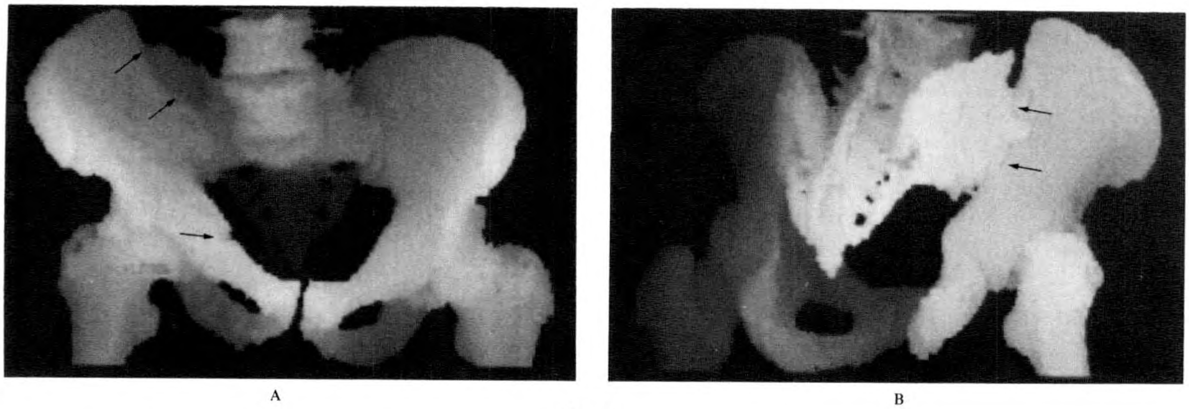

FIG. 5.

Fractures involving the right ilium and superior pubic ramus (arrows) resulting in pelvic asymmetry. (A) Anterior view. (B) Postero-oblique view.

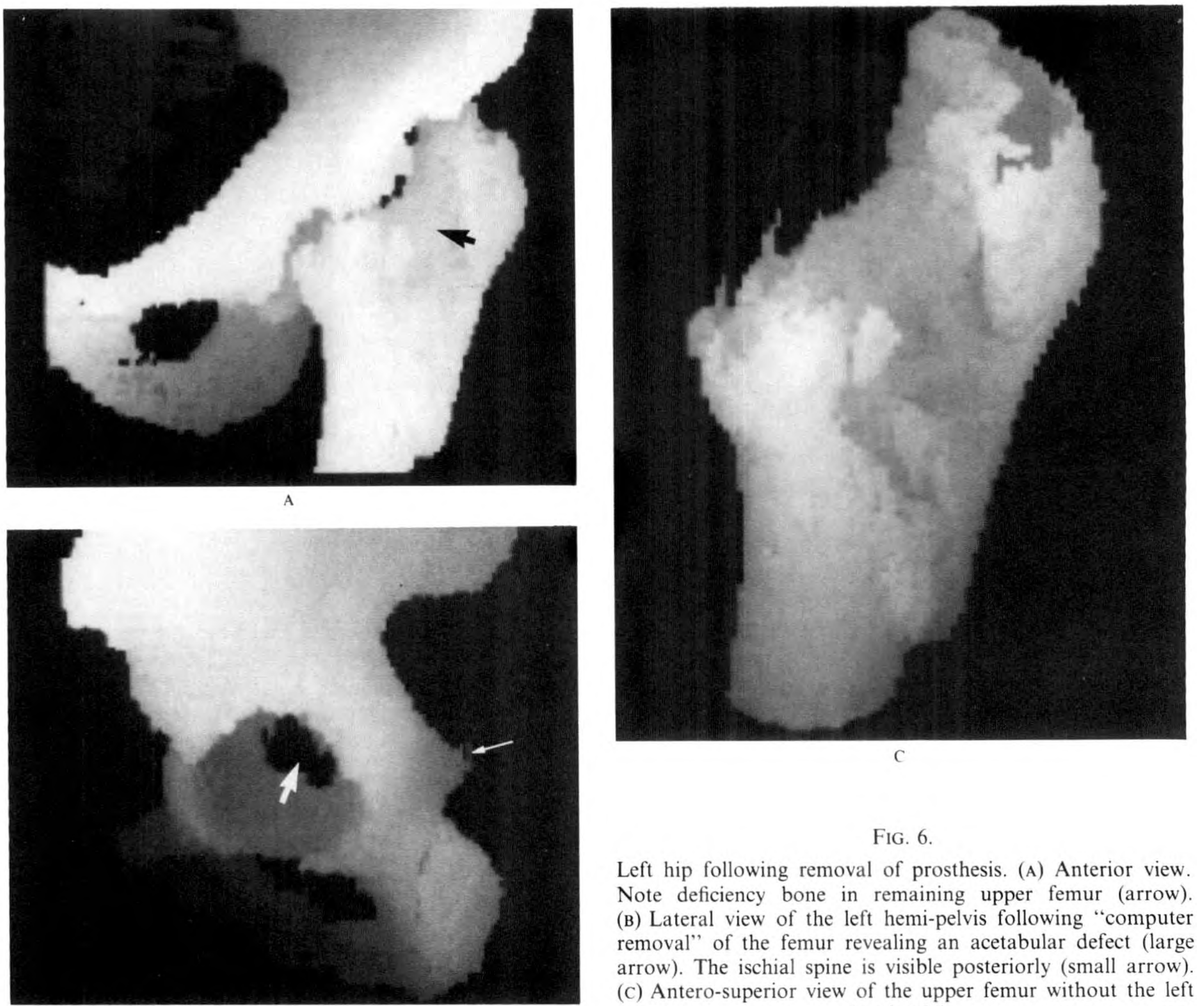

FIG. 6.

Left hip following removal of prosthesis. (A) Anterior view. Note deficiency bone in remaining upper femur (arrow). (B) Lateral view of the left hemi-pelvis following "computer removal" of the femur revealing an acetabular defect (large arrow). The ischial spine is visible posteriorly (small arrow). (C) Antero-superior view of the upper femur without the left hemi-pelvis.

Our continuing assessment of 3D imaging is currently directed towards defining those clinical situations where the technique can most usefully be applied in United Kingdom practice. Topics at present under investigation include: congenital and traumatic skeletal abnormalities involving the head, spine, pelvis and hips; destructive craniofacial lesions; and enhancing intracranial tumours. Experience so far suggests that 3D imaging can offer valuable and sometimes unique information to both radiologist and clinician.

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Ultrasound of the painful hip in children

By R. J. Peck

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(*Received June 1985*)

The condition of "irritable hip" is well recognised in children and is probably the result of a transient synovitis of uncertain origin. It usually occurs in the under-10 years age group and is a benign condition which settles with bed-rest and analgesia. The synovitis causes an effusion and the diagnosis of "irritable hip" is retrospective when the effusion and symptoms have resolved.

The radiological signs of irritable hip are non-specific. "Stand-off" of the femoral head from the acetabulum may occur in children with an effusion, but rotation of the femur can also produce this sign. Evidence of soft-tissue, or capsular, displacement has been shown to be more of a radiological artefact than a true sign (Brown, 1975). This report suggests that ultrasound is a useful additional method of imaging the hip joint in children with a painful hip.

METHOD

Seventy children presenting with a painful hip were examined by both a plain radiograph of the pelvis, and real-time ultrasound of the hips. A 5 MHz sector scanner was used in all the ultrasound examinations. The child was examined in the supine position with the legs straight and the feet together. The normal hip was scanned first to establish a baseline with the scanning plane anteriorly along the femoral neck. The structures visualised are shown in diagrammatic form (Fig. 1) and in a normal ultrasound scan (Fig. 2).

RESULTS

Of the 70 patients scanned, 29 demonstrated the presence of an effusion by a wide echo-free (dark) area between the capsule and the femoral neck (Fig. 3); comparison was made with the symptom-free hip.

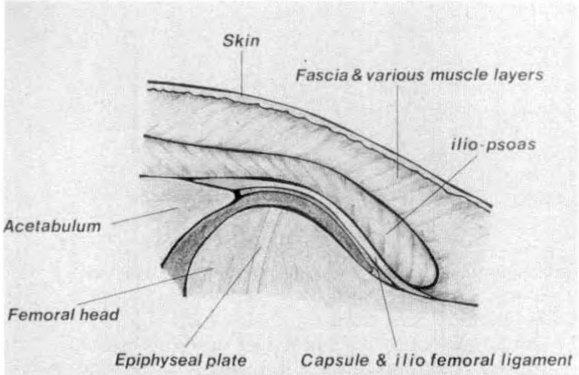
Skin
Fascia & various muscle layers
ilio-psoas
Acetabulum
Femoral head
Epiphyseal plate
Capsule & ilio femoral ligament

FIG. 1.

Anatomical diagram of structures in the plane of the scan.

Of the 29 children with abnormal scans, 12 showed evidence of stand-off on radiography and in only three of these was it thought that there was soft-tissue evidence of an effusion. There were no positive radiographs with negative scans. Two of the 12 also had a pyrexia and a raised white-cell count. Ultrasound demonstrated an effusion, diagnostic aspiration was performed and septic arthritis was confirmed.

One child attended again 2 months after an initial episode of hip pain which had resolved. Radiography had originally shown slight stand-off and, as the episode had settled, the diagnosis of irritable hip was made. Ultrasound was not carried out on that occasion. At the second presentation, ultrasound showed an effusion and an irregular femoral head. Figure 4 shows the irregular head. The diagnosis of Perthes' disease was suggested and further radiography confirmed this.

DISCUSSION

As aspiration was not routinely performed in this study, false positive diagnoses cannot be excluded. Wilson et al (1984), however, found effusions in all hips aspirated which

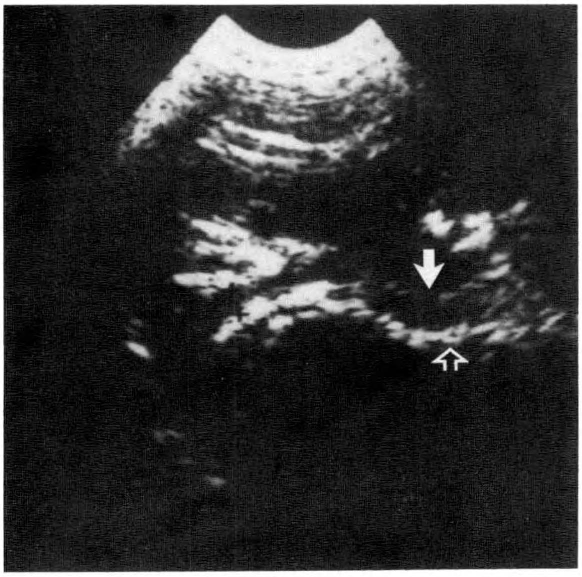

FIG. 2.

Ultrasound scan of normal hip. Femoral neck-line (open arrow). Capsule of joint (solid arrow). The capsular line lies adjacent to, and follows the shape of, the femoral neck.

1986, *The British Journal of Radiology*, 59, 294–295

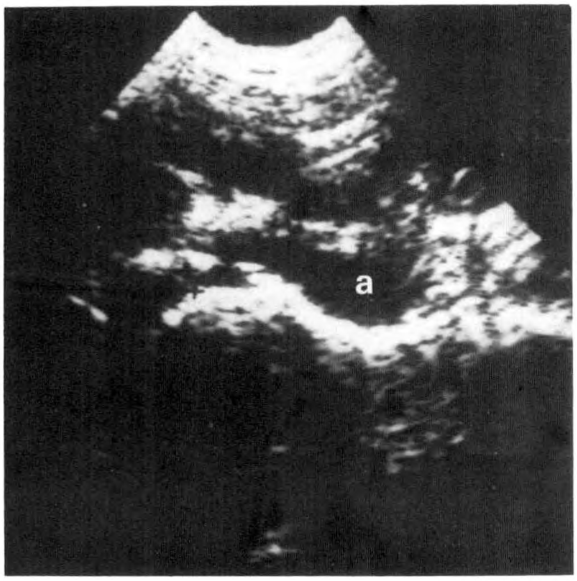

Fig. 3.
Dark area (a) represents effusion.

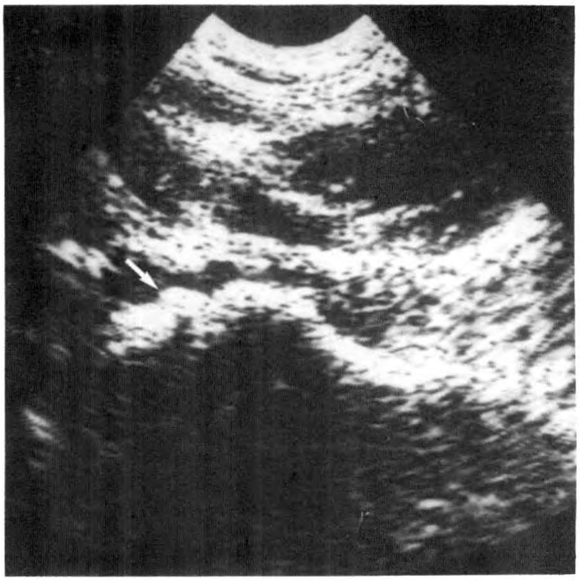

Fig. 4.
Arrow indicates irregular surface of femoral head.

had a "positive" scan. Conditions such as septic arthritis and Perthes' disease must be differentiated from the "irritable-hip". Raised white-cell count and pyrexia suggest the presence of sepsis, and diagnostic aspiration should be carried out. This may be helped by ultrasound confirmation of an effusion. It is not known whether there is an effusion detectable by ultrasound in the early stages of Perthes' disease. Unresolving hip pain obviously requires additional investigation by radiography and/or radionuclide scan.

Ultrasound is a useful additional method of imaging the hip joint. Soft-tissue changes are identified which are not as clearly recognised by radiography. The confirmation of the presence of an effusion is also helpful if diagnostic aspiration is being considered.

Acknowledgment

I would like to thank Dr G. M. Steiner for his guidance and encouragement in the work described above.

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Patients' complaints after barium enema

By J. G. B. Russell

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Patients make complaints after barium enema examinations. This review was done to assess the frequency of these problems. A questionnaire was sent to 65 patients who had had a barium enema as an out-patient. They had been prepared for the examination by taking only clear fluids from the morning before the examination until after the examination, with two doses of sodium picosulphate, 10 mg with magnesium citrate (Picolax, Nordic Pharmaceuticals) given in the morning and the afternoon of the day before the examination. A double-contrast examination was carried out routinely.

Two questions were asked.

(1) Did you have any trouble getting rid of the barium—that is to say, did it make you constipated?

(2) Did you have any trouble with soiling of your clothing after the examination?

The patients were also asked for their comments.

The results are shown in Table I. The majority of patients

TABLE I

COMPLAINTS AFTER BARIUM ENEMA (56 RESPONDENTS)

No complaints	31
Constipation	20
Soiling of clothes	14
Diarrhoea	2
Rectal bleeding	2
Piles	2
Difficulty in flushing barium faeces from the toilet	6
Abdominal pain	5
Vomiting	1

had no complaints. Difficulty in getting rid of the barium was reported by 34%. The normal period of transit of faeces through the large bowel is 2–3 days (Cummings et al, 1976). After the bowel has been cleared by purgation a further movement need not be expected for some days. During this period barium residues will dehydrate and become hard

One quarter of the patients complained of soiling of clothes. There were vehement descriptions of spoilt clothing and car seats. The rectum is skilled at distinguishing flatus from faeces, but the distinction of fluid from air is less certain. After the initial evacuation, the rectum will refill with fluid and air, and attempts at farting lead to soiling.

The frequent passage of stools during preparation for the examination may produce problems with haemorrhoids. All the patients complaining of rectal bleeding and diarrhoea had these symptoms before the examination The five patients who complained of pain after the examination had diverticular disease: with one patient the pain was severe enough for her to seek medical help

Six patients had trouble in flushing the barium stool from their toilet. It is possible that more had this difficulty as they had to "write in" this complaint. Whilst it may seem a frivolous matter, and a criticism of plumbing rather than medicine, it must have been an embarrassment: descriptions were given of the stool lying in the lavatory pan for days.

In a class by herself was the elderly lady who asked when "the electricity will be removed". Apparently a neighbour had a barium enema examination followed by sigmoidoscopy. This last examination had been rationalised as a "removal of electricity".

CONCLUSIONS

A stool-softening laxative, preferably acting by water bulking, such as 20 ml of lactulose, should be given after a barium enema This should stop stool-hardening, increase the rate of passage of the barium and reduce the difficulty in flushing the stool away. Patients should also be told specifically not to attempt to "break wind", unless they are seated over a toilet, for 6 hours after an examination.

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Manual of Radiographic Interpretation for General Practitioners. WHO Basic Radiological System. P. E. S Palmer, W. P. Cockshott, V. Hegedüs and E. Samuel, pp. 216, 1985 (World Health Organisation, Geneva), Sw.Fr.23.
ISBN 92-4-1541776

The World Health Organisation has developed a "Basic Radiological System" to provide improved radiological services in underdeveloped areas of the world. This manual has been produced to help in the interpretation of radiographs in areas where radiological expertise is lacking. The authors selected to compile this manual have vast experience of teaching and of radiographic and radiological problems world-wide. Consequently the manual is an appropriate and first class production.

It commences with warnings on the dangers of radiation to the operator, with less stress on the possible dangers to the patient, which are probably minimal in the prevailing environment. However, the possible dangers to the patient from the administration of contrast media are clearly indicated and the preliminary precautions well documented. The treatment of mild and severe reactions are clearly stated and illustrated.

The main part of the manual is on the radiological interpretation of diseases of the chest, spine, skull, skeleton, abdomen, and urinary tract. Trauma is also discussed. There is a section on obstetric radiography, indicating the lack of availability of ultrasound facilities.

The material is excellent and the reproductions of the radiographs are superb. Common diagnostic pitfalls are indicated and good advice is given with particular emphasis on the importance of clinical examination and the complementary nature of radiological investigation.

This manual is recommended by the reviewer to medical students and DMRD post-graduate trainees, as well as, of course, to general practitioners.

I. H. GRAVELLE

Double-contrast Radiology of the Oesophagus. By Gilberto Rossetti, pp. 154, 1985 (Piccin Nuova Libraria, Padova, Italy), Lire 70 000.
ISBN 88-299-0144-X

This is a handsomely illustrated book which is really an atlas of double-contrast radiology of the oesophagus rather than a formal text. It consists of an opening chapter in which the author describes his technique for obtaining high quality double-contrast views of the oesophagus, within which he stresses the need for hypotonia. Double contrast is obtained both with and without a naso-oesophageal tube, the latter requiring a feeding cup and through which air is pumped at a constant pressure. This is followed by a chapter on the normal oesophagus, and then five chapters on pathological processes involving the oesophagus. The disease processes are well illustrated and particular attention is paid to minimal radiographic signs, many of which would often be overlooked. Indeed, this is the book's particular strength, because it teaches the reader to pay attention to every minor deviation from normal, each one of which may indicate significant pathology. All the abnormalities are well illustrated and each chapter has a few line diagrams in its introduction to guide the reader on to the appropriate appearances shown on the radiograph. Being an atlas, this is really a book to browse through and admire the illustrations rather than to use as a text book for reference purposes. It is, however, well worth while reading if only to make one aware of the potential accuracy of good double-contrast radiology of the oesophagus. At around £28.00 it is extremely good value for money, and I would recommend its purchase for X-ray department libraries as well as the personal collection of interested radiologists.

ALAN H. FREEMAN

1986, *The British Journal of Radiology*, 59, 297–298 MARCH 1986

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

Rationale for lung ventilation imaging

THE EDITOR—SIR,

In a recent article Nimmo et al (1985) compared the economics of ^{127}Xe, ^{133}Xe and ^{81}Kr^{m} for routine lung ventilation imaging. They concluded that ^{127}Xe is the radiopharmaceutical of choice. The criteria for use of ^{123}Xe and ^{133}Xe were quite different, and we would like to comment on the rationale behind the use of radioactive gases for ventilation imaging.

They state that, when using ^{133}Xe, it is essential to perform the ventilation scan before the ^{99}Tc^{m} macroaggregated albumin perfusion study. This is only true if both scans are performed during the same patient visit. It is our practice to perform a ^{133}Xe ventilation study the next morning if the perfusion scan is abnormal. A provisional report based on the perfusion scan and chest radiograph is given immediately and a final report the next day. Some might argue that ventilation disorders causing perfusion defects could change overnight (Neumann et al, 1980), but in practice we do not find this to be a problem. Nimmo et al selected patients for ^{133}Xe ventilation imaging if they had an abnormal chest radiograph. It is our view that this approach is likely to lead to overdiagnosis of pulmonary embolism because we sometimes see matching segmental defects on perfusion and ventilation with a normal chest radiograph. This appearance is usually due to airways disease (McNeil, 1976; Alderson & Line, 1980) but Nimmo et al would report probable pulmonary embolism without the benefit of the ventilation scan.

In their ^{127}Xe protocol, Nimmo et al state that a ventilation scan was *not* performed if there was "...at least one definite segmental perfusion defect not corresponding to a radiological abnormality". Our preceding comments apply to this approach. We also infer that a ^{127}Xe ventilation scan *was* performed when there *were* matching perfusion-scan and chest-radiograph abnormalities. The conventional view is that it is in precisely these circumstances that a ventilation scan is usually not required. Matching radiographic and perfusion-scan abnormalities are usually not due to pulmonary embolism (Biello et al, 1979).

On the question of economics, ^{127}Xe is significantly more expensive than ^{133}Xe at present, and the question for users of radioactive gases is whether the ability to perform perfusion and ventilation scans at the same sitting and the "subjective improvement in image quality" is worth the extra cost.

Yours, etc.,
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(*Received July 1985*)

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(*Authors' reply*)

THE EDITOR—SIR,

In reply to Cosgriff and Berry, we would like to make the following comments.

If ventilation scintigraphy is performed the day after abnormal perfusion images are obtained, there is a delay of 15 to 24 h before a definite report can be issued. We consider this to be unacceptable in the investigation of probable pulmonary emboli. Furthermore it is necessary to repeat the perfusion scan after ^{133}Xe ventilation to exclude definitely (or definitely confirm) V/Q mismatch. The ventilation pattern can alter rapidly, for example as the result of mucous plugs, and it is not reasonable to compare the distribution of ventilation with that of perfusion 18 h or so earlier. An apparently matched V/Q defect may have been a mismatch at the time of initial presentation (or vice versa). The former would lead to underdiagnosis of emboli, which is much more worrying than slight overdiagnosis of this condition, for which safe treatment is available. Use of ^{127}Xe overcomes both of these problems.

In view of the above, unless an unequivocally normal chest radiograph is used to select patients, it is necessary to ventilate all patients prospectively with ^{133}Xe to avoid overdiagnosis of pulmonary emboli. This influences the economic comparison significantly in favour of ^{127}Xe. The criteria used to define normality are important. Absence of consolidation or of collapse do not of themselves imply normality. If (as we indicated in our paper) the criteria for a normal chest radiograph are very strict and "...at least one definite segmental perfusion defect not corresponding to a radiological abnormality" is found, then overdiagnosis is unlikely to be significant. "Segmental" is of the essence. Obstructive airways disease does not produce segmental defects. If it is not possible to name the bronchopulmonary segment involved, ventilation is essential for proper differential diagnosis. Where perfusion defects exactly matched radiographic abnormalities a ventilation scan was not performed, as there is no evidence that in this case it assists in the differential diagnosis between infection and infarction.

^{127}Xe is more expensive per unit of activity than ^{133}Xe, but our point was clearly stated that fewer patients required ventilation with ^{127}Xe. This, together with the longer shelf life

1986, *The British Journal of Radiology*, 59, 298–299

(due to longer half-life), resulted in less ^{127}Xe being ordered to provide the same level of service. Overall costs for the radiopharmaceuticals were similar, but considerable savings are evident when the cost of camera time and ventilation bags are taken into account. We did not analyse the "subjective improvement in image quality", which is irrelevant to the economics of the case. The reduced population exposure to radiation must also be desirable

Our conclusion, that ^{127}Xe is the radiopharmaceutical of choice for routine lung ventilation scintigraphy in adults, remains valid

Yours, etc.,
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(*Received September 1985*)

Economics of xenon 127, xenon 133 and krypton 81m for routine ventilation imaging of the lungs

The Editor—Sir,

We would like to comment on the paper by Nimmo et al (1985) on the economics of ^{127}Xe, ^{133}Xe and ^{81}Kr^{m} for routine ventilation imaging of the lungs. We take issue with their approach to ventilation-perfusion (V/Q) imaging. Although the vast majority of patients are referred because of a question of pulmonary embolic disease, surely this should not be a reason for limiting the examination in the way in which the authors advocate. A V/Q scan should image regional ventilation and perfusion in an attempt to elucidate the patient's symptoms; it should be a complete examination and not limited to views of the back of the patient. To support this view, perhaps we might make the following points.

A segmental defect of perfusion in a patient with a normal chest radiograph is not diagnostic of pulmonary embolic disease. Airway obstruction, as in asthma or chronic bronchitis, may be segmental and may cause either a matched defect or a perfused non-ventilated lesion.

Secondly, a normal perfusion scan, while excluding pulmonary embolic disease, does not imply the absence of focal lung disease, the patient may have extensive pneumonic consolidation, airway obstruction, or collapse (Lavender et al, 1981). Hypoxic vasoconstriction is not always very effective in man.

Turning to the comparison they make of the three techniques of ventilation imaging, although the article is concerned with economics, some regard for value for money must be implied by such a title The technetium aerosol scans are dismissed as too much work (although cheap)—they do, however, provide a complete set of lung images, not just the back view, as is the case with xenon. Our experience is that diagnostic abnormalities are almost always best seen in posterior, oblique views. In a review of 50 patients in our department with pulmonary vascular occlusion, V/Q mismatch was present only in oblique views in 38%. Furthermore, in a review of 50 consecutive lung scans, 15% of patients who had normal posterior ventilation images had abnormalities on oblique views, and 25% of patients with abnormal posterior images had additional ventilatory defects on the oblique views. It seems clear to us, therefore, that a limited study of ventilation may lead to overdiagnosis of pulmonary embolism by missing ventilatory defects visible on other views. In addition, comparable images of ventilation and perfusion readily obtained with ^{81}Kr^{m} may often enable a diagnosis of pulmonary infarction where ventilation is less impaired than perfusion in the presence of radiographic consolidation.

Krypton 81m is the "gold standard" for V/Q scanning. Are the costs so impossibly high? In our view V/Q imaging does not need to be available at all times Except in the rare patient where a contraindication arises to anticoagulation, heparin can be started until the diagnosis is confirmed, or refuted. This allows for the efficient use of a krypton generator for a large number of patients, and of course if used in this way, krypton is in actual fact much cheaper than the alternative radioactive gases. The cheapest is, of course, still the aerosol.

Nimmo et al should push for the right tool and not make do with less.

Yours, etc.,
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(*Received August 1985*)

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(*Authors' reply*)

The Editor—Sir,

We would like to take the opportunity of refuting the letter by Lavender and Finn. We wholly disagree with every one of their statements, which we believe perpetrate a number of serious errors, misquotations and misunderstandings, not only of what we have written, but also of the previous literature. These should not go unchallenged.

As we explicitly stated, one of the important advantages of ^{127}Xe is that an optimal projection for the ventilation study can be chosen from the perfusion study, thus eliminating the choice of a standard posterior projection. There is no evidence that, when this procedure is followed, multiple projections increase diagnostic accuracy. It is, of course, theoretically possible that a patient may have multiple perfusion defects, only some of which are due to recent emboli. There is no reason why such cases should not be given a second breath of ^{127}Xe if all defects visualised on the first chosen are matched. In practice, this is a sufficiently rare phenomenon (we have yet to encounter it) not to alter the economic arguments.

We are taxed for not performing a "complete" examination. We would suggest that it is Lavender and Finn who never perform a complete examination. There are three parts to a ventilation study: wash-in, when the count rate is a function of ventilation; equilibrium, when it indicates lung volume, and wash-out, when it shows air trapping. All three are required

1986, *The British Journal of Radiology*, 59, 299–301 MARCH 1986

Correspondence

for proper interpretation. The count rate from a patient breathing ^{81}Kr^m at equilibrium is claimed by Lavender and Finn to indicate the first of these. In fact, as Fazio and Jones (1975) pointed out, this is an approximation valid only under the special condition that the respiratory rate is slow or normal. As the respiratory rate rises the observed count rate increasingly includes a contribution from lung volume. Patients with pulmonary emboli commonly are tachypnoeic. The images obtained with ^{81}Kr^m are thus influenced to variable extents by both ventilation and volume, unlike the first-breath xenon image which is purely ventilation dependent. The latter two phases cannot be studied adequately with ^{81}Kr^m because of its short half-life and they are ignored by Lavender and Finn. It is impossible to perform a "complete" study with ^{81}Kr^m. A further advantage of a 10 s image of the first breath is that movement artefact, which is much greater than is often appreciated, is minimised.

We did not claim that segmental defects of perfusion in a patient with a normal chest radiograph were "diagnostic" of pulmonary embolism. The probability of emboli being the cause is high, in most reported series greater than 90%. In the real world, absolute certainty is rarely attainable. It is a matter of clinical judgement what level of confidence is required to determine management. Airway obstruction is readily detectable during the wash-out phase. Our paper concentrated on the only common indication for lung scintigraphy in clinical practice, namely the acute detection of pulmonary embolism. Documentation of chronic lung disease, which is usually well known to the referring clinician and is unlikely to alter management, is an academic exercise of minimal value. The statement that "patients with extensive pneumonic consolidation . . . or collapse" may have a normal perfusion study is relevant only if the scintigraphic examination is viewed in isolation, a practice we explicitly condemned.

In any individual case the decision whether or not to perform a ventilation study is determined by the complete clinical picture, not arbitrary rules. The guidelines outlined in our paper summarise a reasonable starting position, but it is neither possible nor useful in a short paper to enter into a detailed philosophical discussion of what ultimately will always be a subjective value judgement.

Regarding the use of aerosols, we repeat that we do not advocate a standard posterior view. Lung volume and wash-out cannot, of course, be studied by aerosols, and aerosol ventilation studies are most likely to be technically unsatisfactory in patients with pre-existing lung disease—a group in whom an inconclusive perfusion study is very common. Aerosols are, moreover, technically more difficult to set up, requiring more than one pair of hands to operate. This can be a problem, especially at night and at weekends when no technicians or radiographers are available. Indeed, does any department offer a 24-hour 7-day emergency service using aerosols? We have provided such a service, using initially ^{133}Xe and more recently ^{127}Xe, for over 11 years, having only a single person on call at a time. The cost of requiring even a second person on call will certainly outweigh the cost advantage of ^{99}Tc^m.

There are about 500 hospitals in the United Kingdom with gamma cameras, and therefore presumably providing a clinical service. There is not the remotest possibility of providing regular supplies of krypton generators even once a week to such a number. Ventilation-perfusion mismatch is a relatively fleeting phenomenon following pulmonary embolism. In most cases it is resolved within 48 h. Ventilation scintigraphy later than this consequently often fails to assist in differential diagnosis. If the examination is worth performing at all it must be in time to influence management. If patients are to be anticoagulated notwithstanding, scintigraphy is not being used properly, but as a luxury.

Finally, we are amazed that an incomplete examination, often performed so long after the acute event as to be of necessity inconclusive, should be arbitrarily set up as a "gold standard". What evidence do the authors have for such a claim?

Yours, etc.,
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(*Received September 1985*)

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Glutathione depletion: does it influence radiosensitisation by misonidazole?

THE EDITOR—SIR,

In your April issue, two distinguished groups of radiobiologists expressed diametrically opposed views on glutathione (GSH) depletion and misonidazole (MISO) efficiency (Brown & Bump, 1985, Shrieve & Denekamp, 1985). I would like to offer some suggestions which might lead to a resolution of this conflict.

Firstly, there are questions of semantics. How do we define "additive", a word which Brown and Bump use on six occasions? "Additive" sounds simple enough, but unfortunately this expression is dangerously ambiguous (Scott, 1961). It can be used to describe (A) similar joint action, or (B) independent joint action (Goldin & Mantel, 1957). The fuzziness surrounding the idea of additivity was encapsulated in the "Envelope of additivity" by Steel and Peckham (1979). Note that Goldin and Mantel's type B corresponds to Steel and Peckham's Mode 1.

There is a profound difference between the two types of additivity. To give an example familiar to radiobiologists; X rays generated at, say, 250 kV and 251 kV would be found to be additive in the sense of "similar joint action", whereas α particles and X rays may be additive in the sense of "independent joint action" if the survivors of α-particle radiation respond to subsequent doses of X rays in precisely the same way as untreated controls (Barendsen et al, 1960). Brown and Bump ask what would be expected if GSH depletion and MISO sensitisation were "truly" additive. Perhaps they have unconsciously assumed that Goldin and Mantel's type A is the only true additivity?

On the other hand, Shrieve and Denekamp propose what is in effect independent joint action to describe the interaction of buthionine sulphoximine (BSO) and MISO. If the actions are indeed totally independent, then multiplication of the separate enhancement ratios, which Shrieve and Denekamp propose, is

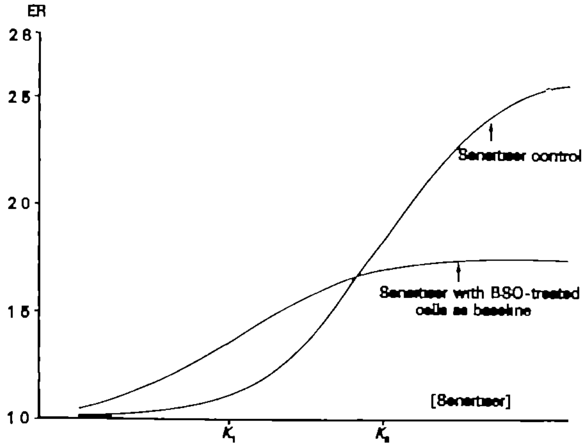

FIG. 1

Enhancement ratio (ER) plotted against sensitiser concentration. Theoretical curves obtained by application of the "x" model (Edgren et al, 1985) to the data of Bump et al (1982), normalising the 5% GSH depletion curve by division by 1.5. The K values for control and BSO-treated cells are K_1 and K_2 respectively.

the correct procedure. On present evidence, it seems likely that the BSO–MISO interaction cannot be accurately described either as an example of type A or type B additivity. I suggest that we abandon the attempt to find one word to describe the interaction, but rather we set up a hypothesis of the type "If such and such a version of the competition hypothesis is correct, then we would expect so and so" and test the predictions of a rigorously defined model against experimental data. In this way we may avoid sinking in a morass of semantics.

Unfortunately, there is a further semantic point to be cleared up; the definition of "efficiency". Presumably, we would all agree that a sensitiser which was effective at low dosage is more efficient than one requiring a high dosage, *i.e.* we think of oxygen as more efficient than MISO because the K value is so much lower? But we can also compare the theoretical enhancement ratio at infinite sensitiser concentration (m) if we assume that the Alper-Howard-Flanders relation holds. Suppose two sensitisers have the same K value, but one gives $m = 3$, and the other $m = 1.5$, would we not regard the former as more efficient?

Now let us consider the K curves for a sensitiser using BSO-treated or control cells. If we follow the important suggestion of Shrieve and Denekamp, and plot the enhancement ratio (ER) of BSO-treated cells normalised to unity at zero sensitiser concentration, we might obtain the result in Fig. 1. Has BSO increased the efficiency of MISO? In so far as K is reduced, efficiency is increased, but if m is reduced, then efficiency is reduced! I submit that if the facts are as shown in the figure, then the concept of "efficiency" breaks down completely.

Is the figure a fair picture? Crossing curves are shown in Shrieve et al (1985) (their Fig 6) for oxygen, but not for MISO. At this stage I would prefer to return this question to the experimentalists; do the curves cross?

Shrieve and Denekamp suggest basing the comparison of control and BSO-treated cells on the measurement of the dose of sensitiser to obtain an ER of 1.7. If the curves cross as shown, then the result will depend entirely on this arbitrary choice of 1.7. If a lower ER, say 1.3, had been chosen, then BSO would have appeared to increase the "efficiency" of MISO (as so defined). If 200 had been chosen, BSO would have rendered MISO ineffective!

The proposed plot of Brown and Bump (their Fig 2) is perhaps open to the same objection—that the factor of increased MISO efficiency depends on an arbitrary choice of an ER of 1.5.

In summary, I suggest we abandon the attempts to define "additivity", and "efficiency", but concentrate instead on asking the question, do our models of radiation action fit the data? In this connection it is encouraging that the 'x' model of Edgren et al (1985) appears to fit the classic studies of Dewey (1963) using Serratia Marcescens and cysteine protection with parameters $x = 6.72$, $F/S = 088$, $K = 0.1\%$, $m = 5$ and $R = 20$.

Yours, etc.,
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(*Authors' reply*)

THE EDITOR—SIR,

In his thoughtful letter Scott points out the confusion that can arise from the terms "additivity" and "efficiency" when applied to the radiosensitisation produced by GSH depletion and its influence on radiosensitisation by MISO. The earlier publication of Shrieve and Denekamp (1985) suggested that the hypoxic radiation survival curve of the GSH-depleted cells (by BSO treatment in the example used) is the appropriate control from which to evaluate the efficiency of radiosensitisation by MISO. In effect, this is to multiply the individual sensitiser enhancement ratios (SERs). Using this method they concluded that GSH depletion does not enhance the efficiency of MISO. We, on the other hand (Brown & Bump, 1985), pointed out that the expected joint SER for GSH depletion and MISO, if the two were "truly additive," would be much less than the product of the individual SERs. As we emphasised, this is a consequence of the fact that the SER for MISO rises approximately linearly with the *logarithm* of MISO concentration.

Scott is correct in pointing out that the essential difference between the Shrieve and Denekamp and Brown and Bump analyses is in the definition of "additivity." Scott notes, "additivity" can mean "similar joint action" or "independent joint action." As we illustrate below, the mechanism of the interaction will determine the correct way to analyse the data.

If there is good reason to believe that two agents act independently, then it is correct, as Shrieve and Denekamp suggest, to multiply the individual SERs. Such an example would be radiosensitisation of hypoxic cells by the pyrimidine analogue bromodeoxyuridine (BrdU) and MISO. If the maximum SERs for each were 2.0 and 2.8 respectively, we would expect a combined maximum SER of the product of the two, or 5.6. Further, the baseline for radiosensitisation by MISO of BrdU-treated cells should be the radiosensitised BrdU cells. This is what Shrieve and Denekamp propose for BSO-treated cells.

On the other hand, if there is reason to believe that the two agents have a similar joint action, the above analysis would be wrong. For example, adding two concentrations of MISO each of which produces an SER of 2.0 would not yield an SER of 4.0. This was the main point of our letter (Brown and Bump, 1985).

Thus, how the analysis should be performed depends on whether the evidence favours independent or similar joint action. In the absence of any knowledge of the interactions, it would be fair to perform both types of analysis, in essence, forming the boundaries of the "envelope of additivity" defined by Steel and Peckham (1979).

We suggest, however, that such is not the case: the evidence favours a similarity of radiosensitisation by GSH depletion (by BSO or other agents) and radiosensitisation by electron-affinic agents (by MISO or other nitroimidazoles). Both act primarily on hypoxic cells, and most importantly, the combination of the two does not produce greater radiosensitisation than the maximum radiosensitisation by MISO alone (the OER). Our point, therefore, is that the implicit assumption of independent action in the Shrieve and Denekamp suggestion of normalising the SER of BSO-treated cells to unity at zero MISO concentration, cannot be justified. It leads to what we believe are too high expectations for the SER of BSO and MISO combined and ultimately to Shrieve and Denekamp's conclusion that GSH depletion does not increase the efficiency of MISO.

We do not mean to imply that the basic competition model is 100% accurate in describing the interaction of MISO and GSH depletion. That there is competition seems clear from the bulk of the data, and Scott himself has shown that the modified competition model of Koch and Howell (1981) gives an excellent fit to data in the literature of GSH depletion and MISO efficiency (Scott, personal communication, 1985).

In his letter Scott suggests that in addition to the definition of "additivity" there is also a problem with the word "efficiency" in relation to radiosensitisation. His example of two sensitisers with the same K value but different maximum SERs (m values) would certainly produce a problem if "efficiency" was defined solely on the K value. But is this a realistic example? Few, if any, hypoxic cell radiosensitisers have lower m values than MISO. Further, his example of BSO reducing the m value for MISO (his Fig. 1) is a result of what we suggest is the inappropriate normalisation of the BSO-treated cells to an SER of unity. The same procedure with MISO-treated cells would produce the conclusion that one dose of MISO would reduce the m value for a second MISO dose. Thus, while agreeing that we should cease arguing over "additivity" and focus instead on whether a particular model fits the data, we feel that radiosensitiser "efficiency" defined (usually) as the drug concentration required to produce an SER of 1.6 ($C_{1.6}$) is a useful and important concept in the field, and should continue to be used.

In summary we agree with Scott that the two methods exemplified by Shrieve and Denekamp (1985) and ourselves for analysing the combined use of BSO and MISO depend on the implicit assumption of either independent or similar joint action respectively, and that these are two equally justifiable ways of defining "additivity." However, we believe that the available data do not support independent radiosensitisation, and therefore using BSO-treated cells as the control for MISO radiosensitisation, as proposed by Shrieve and Denekamp (1985), is contraindicated.

Yours, etc.

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Inadvertent buckling of caesium-137 needles—a cautionary tale

THE EDITOR—SIR,

Caesium-137 needles, intended for implantation into patients, are sterilised before use by autoclaving. For this purpose, a shallow metal tray and special needle carrier were made. The carrier consisted of a polypropylene block (115 mm × 115 mm × 24 mm), into which 13 troughs had been milled, using flat-ended cylindrical cutters. Seven long troughs (nominal dimensions 69 mm long, 15 mm wide, 19.4 mm deep) were intended to carry threaded needles of 55 mm external length (Amersham International CDCS A3 and B3), and six short troughs (nominal dimensions 54 mm long, 10 mm wide, 19.4 mm deep) were to carry needles of 24.5 mm, 32 mm, or 40 mm external length (Amersham International CDCS A1, A4, A2 and B1, B4, B2). The caesium 137 in CDCS needles is doubly encapsulated in stainless steel (AISI 316L).

The Sealed Sources Laboratory received a request for 10 A3 needles and six B3 needles, that is, for two sets of needles of different activity but the same external length of 55 mm. The two types of needles were, as usual, distinguished by the colour of their threads, but it was decided to segregate them in the carrier by placing the A3 needles in the long troughs and the B3 needles in the short troughs. Prior to autoclaving, each of the six B3 needles was placed in a trough, with the trochar point at one bottom corner of a trough, and the other end of the needle resting against the opposite wall of the trough. The metal tray and loaded needle carrier were then autoclaved for 20 min at 121°C.

After the implantation, two unused B3 needles remained in the carrier. However, they were no longer leaning at an angle along the trough, but were lying on the bottom of the trough, and were noticeably bent at about 4 mm from the trochar point. The needles were tightly fixed in this position and when extricated and examined, it was found that the outer wall of both needles had buckled at the bend. Although leakage of caesium 137 had not occurred, no attempt was made to straighten the needles because of the buckling. They were taken out of service and set aside for eventual replacement.

In retrospect, it was evident that the difference between the thermal coefficient of expansion of stainless steel ($1.7 \times 10^{-5}/°C$) and that of polypropylene ($2 \times 10^{-4}/°C$) was the root cause of the damage to the needles. During autoclaving, the short troughs (nominal length 54 mm) expanded sufficiently to allow the inclined needles to fall to a horizontal position at the bottom of the trough. On removal from the autoclave, the polypropylene then cooled and contracted, with the result that two of the needles were cramped along their length and eventually buckled at their weakest point.

The actual overall lengths of the six troughs measured 53.52 mm, 53.54 mm, 53.68 mm, 54.05 mm, 54.12 mm and 54.22 mm, and it was in the two shortest troughs that the trapped and buckled needles were found. The other four B3 needles were used in the implant, and, when, subsequently examined, all were found to have some surface marks, two were slightly bowed along their length and one was slightly bent at the eyelet end. None showed evidence of leakage of caesium 137, and all four were considered fit for future use.

It is difficult to avoid the conclusion that the incident was a manifestation of Murphy's Law ("that which can possibly go wrong, eventually will"). Had the length of the short troughs been greater than about 55 mm, the B3 needles would have lain on the bottom of the trough at room temperature, and would have suffered no stressing at all due to differential expansion and contraction. Had the trough length been less than about 51 mm, the inclined needles would have projected above the top surface of the carrier in an unacceptable manner.

The conclusion is clear. A radioactive clinical source should never be subjected to autoclaving whilst it is resting in an inclined position in a cavity within any rigid material.

Yours, etc.,
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Chairman: Professor L. A. Gillanders

The development of a RF hyperthermia system for clinical use, by K. Bartlett
Percutaneous management of intraperitoneal sepsis, by A. P Bayliss
Angioplasty of the aorta, by T. A. S. Buist
Computed tomography and magnetic resonance images in relation to the radiotherapy of bladder carcinoma, by T. K Sarkar and G. McCann
Cytogenetic effects on peripheral lymphocytes of chemotherapy and radiotherapy for lymphoma, by A. A. Dawson and T. Brown
Differences in the incidence of lymphoma in two areas in East Scotland, by M A. Ratcliffe, A. A. Dawson, G. Innes, J. S. Scott and L. Camson
The management of ovarian carcinoma—the Aberdeen experience, by W. T. Fullerton
Magnetic resonance imaging of the musculoskeletal system, by H K. Genant
Balloon dilatation of oesophageal stricture, by J. K. Hussey
Is magnetic field strength over-rated? by F. W. Smith
The gastrointestinal tract–pitfalls and pathology encountered with the use of ultrasound, by P. Morley
Nuclear magnetic resonance in the detection, diagnosis and staging of head and neck cancer, by G. R. Cherryman
Comparison of ultrasound, computed tomography and nuclear magnetic resonance in gynaecological malignancy, by J. F Calder
Computed tomography of the chest in non-malignant disease, by E. M. Robertson
Imaging regional cerebral blood flow with ^{123}I- and ^{99}Tc^{m}-labelled agents, by P F. Sharp
Phenol sympathectomy, by S Sutton
Computed tomography of the chest in malignant disease, by J. Weir
Multimodality treatment for operable carcinoma of the oesophagus, by H. Yosef and R. A. McCluskie
Carcinoma of the breast—adjuvant tamoxifen and chemotherapy, by H. J. Stewart
Adjuvant systemic chemotherapy in breast cancer, by D C Smith

THE DEVELOPMENT OF A RF HYPERTHERMIA SYSTEM FOR CLINICAL USE

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We know, and we have proved locally, that if one exposes accessible human tumours to doses of X rays, and then follow it up 1.5–2 h later with local RF heating to temperatures of the order of 4–5°C above body temperature for 45–60 min, then we can make squamous-cell tumours, melanomas and breast tumours disappear quite rapidly We have the impression that renal-cell carcinomas and soft-tissue sarcomas may also be vulnerable to this kind of attack.

Unfortunately, this is like "winning a battle and losing a war", because of the high metastasing potential of these tumours. After initial experiments (October, 1981 to June, 1982) we have looked around for alternative methods of:
(1) raising the whole body temperature,
(2) raising the temperature of loco-regional areas of the body,
(3) ways of combining (1) and (2) to get a two-stage system operational.
We are only now at the stage of attempting to capitalise on these lines of research

PERCUTANEOUS MANAGEMENT OF INTRAPERITONEAL SEPSIS

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Over the past few years there has been a change in the approach to the management of intra-abdominal abscesses. The development of imaging systems such as CT scanners and "real-time" ultrasound scanners has made the diagnosis of intra-abdominal abscesses far more reliable, and percutaneous aspiration, in selected patients, is fast becoming the method of choice in the treatment of abscesses within the peritoneal cavity or within intra-abdominal organs.

This paper describes our experiences in the management of abdominal abscesses in various sites using ultrasonically guided percutaneous aspiration and/or drainage techniques, and indicates some of the difficulties and problems which may be encountered.

ANGIOPLASTY OF THE AORTA

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Percutaneous angioplasty can be a simple and effective alternative to major surgery in the treatment of abdominal aortic stenosis. At this stage relatively small numbers of cases have been reported. Short or long segments of aortic stenosis can be successfully treated using single or multiple angioplasty balloon techniques.

Atheromatous aortic stenosis most commonly affects the distal abdominal aorta and bifurcation region, and simultaneous bilateral common iliac and aortic angioplasty is then indicated Congenital and post-arteritic stenosis can affect long segments of the abdominal aorta and the origins of branch arteries Although in these conditions the stenosis is initially more resistant to transluminal angioplasty, successful dilatation can be achieved using a staged technique with progressively greater balloon diameters.

The paper discusses the method of assessment and treatment of abdominal aortic stenosis, and the results of aortic angioplasty in 20 cases with follow-up of 10 to 50 months are presented, with special attention to the particular value of this technique in the management of young patients with non-atheromatous abdominal aortic stenosis.

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGES IN RELATION TO THE RADIOTHERAPY OF BLADDER CARCINOMA

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In the first part of this presentation a comparison is made of the respective and relative contributions of CT and MRI imaging in the assessment of patients with carcinoma of the bladder referred for radiotherapy in Aberdeen. The radiologist reporting one type of scan was unaware of the information provided by the other, although the findings on EUA and cystoscopy were available in all cases.

In the second part of the presentation the feasibility of interfacing an MRI scanner with the therapy planner is discussed The object is to obtain accurate patient-contour and target-area data, and to achieve tissue inhomogeneity correction for more accurate isodose plotting using the MRI data

CYTOGENETIC EFFECTS ON PERIPHERAL LYMPHOCYTES OF CHEMOTHERAPY AND RADIOTHERAPY FOR LYMPHOMA

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It is known that cytotoxic drugs, especially alkylating agents, produce cytogenetic damage to peripheral blood lymphocytes. The most sensitive method for demonstrating chromosomal DNA damage and repair is by measuring the frequency of sister chromatid exchanges (SCEs) in standard cell cultures Damage by radiotherapy is detected as standard cytogenetic damage.

In patients with Hodgkin's disease having first-line chemotherapy (MVPP), a pattern for SCE frequency on successive pulses of therapy has been demonstrated, with a progressive rise in frequency until the fifth pulse, followed by a fall. Follow-up of such patients produced a SCE frequency in the normal range.

Patients with lymphoma, having other forms of first-line chemotherapy, have a similar, though sometimes less dramatic, response of SCEs. There is a characteristic response of SCEs within hours of administering the chemotherapy. Difficulties encountered in inducing cell division immediately after chemotherapy are being investigated, both with respect to the T/B lymphocyte ratio, and the presence of a blocking antibody in the serum of some patients with Hodgkin's disease

The pattern of SCE response to chemotherapy seems to be related to the clinical response to treatment. We are investigating it, in the long term, as a possible marker for a second malignant tumour

DIFFERENCES IN THE INCIDENCE OF LYMPHOMA IN TWO AREAS IN EAST SCOTLAND

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In the 8 years (1975–82 inclusive) when there was no systematic rise in the total numbers of patients in Scotland registered as having a lymphoma by the Scottish Cancer Registries, there was an excess of patients with lymphoma in both Grampian and Tayside. The accuracy of these figures for Grampian was confirmed by comparing the Cancer Registry's details for 1981 and 1982 with those recorded by two completely independent local methods organised by the East of Scotland and Newcastle Lymphoma Group (ESNLG) and the Grampian Oncology Research Project (GORP).

Despite Grampian and Tayside being very comparable areas of Scotland, these figures demonstrated that there has been a systematic excess of cases of non-Hodgkin's lymphoma (NHL) and, to a lesser extent, of Hodgkin's disease, in Grampian compared with Tayside. This increase in NHL cases appeared to be most marked in men in the older age group, and in Hodgkin's disease cases appeared to be most marked in both males and females, in the 21–40-year-old range. No factitious cause for this was detected.

Epidemiological studies have suggested that rural areas in general have a higher incidence of various malignant diseases than urban. As Grampian and Tayside have large rural areas, the pattern of incidence of lymphoma was constructed, in relation to density of population per hectare, but no statistical difference in lymphoma was found

Much more detailed work on the epidemiology remains to be performed

THE MANAGEMENT OF OVARIAN CARCINOMA—THE ABERDEEN EXPERIENCE

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In ovarian cancer the standard of recorded data is often poor, staging from the data impossible or imprecise, and treatment is very conservative in the hands of surgeons and gynaecologists. Radiotherapists and oncologists do not have access to many patients they could treat effectively.

With the development of tumour markers and new chemotherapeutic agents, meticulous documentation and strict treatment protocols must be maintained for efficient therapy and for evaluation of results Four hundred and forty-two cases of ovarian carcinoma have been analysed. Methods of improving documentation and standardising treatment are discussed.

A retrospective analysis of 107 patients treated with high dosage oral Treosulfan is presented. It is our conclusion that in selected patients there is a place for single drug oral Treosulfan in the therapy of epithelial ovarian cancer.

MAGNETIC RESONANCE IMAGING OF THE MUSCULOSKELETAL SYSTEM

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Several feaures of magnetic resonance imaging (MRI) make it particularly attractive for musculoskeletal imaging: 1) the superior soft-tissue contrast of MRI relative to that of CT; 2) the ability of MRI to image directly the body in the sagittal and coronal planes, as well as the axial plane, 3) the ability to vary the level of contrast between tissues by manipulating the MRI pulse sequence parameters; 4) the lack of artefacts from beam-hardening effects, and 5) the capacity to image in the presence of metallic hardware.

All subjects included in this review were examined at the University of California, San Francisco, using a Diasonics MT/S imaging system. This system consists of a 0.5 Tesla superconducting magnet which is currently operated at a field strength of 0.35 Tesla. To date, we have acquired all of our images using the spin-echo technique.

MRI is currently a complementary technique to CT in the examination of the spine, the hip and of musculoskeletal tumours. In some cases, it provides diagnostic information not available with any other modality, including CT. MRI has the potential to be very useful in the assessment of various marrow-based disorders, and may some day obviate the need for contrast-aided studies of ligaments, tendons, and cartilage. With further technological advances in magnet and coil design, and improvements in software, MRI will undoubtedly play an ever increasing role in musculoskeletal diagnosis.

BALLOON DILATATION OF OESOPHAGEAL STRICTURE

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Simple interventional techniques in modern radiology are rare. Many interventional techniques are complex and require considerable time and effort on behalf of radiologists, nurses and radiographers. With the development of the balloon catheter, a simple method for stricture dilatation is now available, requiring neither much skill nor time. Effective dilatation of even the most narrow strictures can now be carried out with virtually no risk to the patient.

We commenced dilatation of proven benign strictures of the oesophagus mainly in patients considered unfit for general anaesthesia and conventional oesophageal bouginage. We have carried out approximately 140 dilatations on approximately 100 patients. The majority were peptic strictures, but within this group are included patients with achalasia and a few patients with neoplastic strictures. All dilatations were carried out by the same radiologists. The only major complication was rupture in one patient where circumstances were unusual, but the patient survived his rupture, which was treated conservatively. All patients were given intravenous sedation and analgesia prior to the dilatation. The catheters have balloons of two sizes. The first is a 15 mm diameter, 6 cm long balloon. The second is a 22 mm diameter, 8 cm long balloon. The catheters are purchased from Cook UK Ltd. The technique is extremely safe and can be used in any general radiological practice and provides considerable benefit to patients with dysphagia resulting from oesophageal strictures.

IS MAGNETIC FIELD STRENGTH OVER-RATED?

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The majority of commercial magnetic resonance imaging systems are marketed according to magnetic strength, with less emphasis being placed on other aspects of imaging which are of equal importance. Magnetic strengths offered range between 0.02–2.0 Tesla (200–20 000 Gauss), super-conducting magnets being available throughout the range.

It has been found that there is no significant improvement in spatial resolution at field strengths greater than around 0.6 Tesla when an accompanying fall-off in contrast occurs. Major improvements in image quality during the first 5 years of MR imaging have come from modifications of other factors through the process of image acquisition to final display.

Homogeneity of the field may in fact be more important than the strength of the magnet, super-conducting magnets producing more stable homogeneous fields than resistive magnets.

Significantly improved images, particularly of the orbit, petrous bone, cervical and dorsal spinal cord, are obtained following the application of specialised receiver or surface coils, and through the introduction of cardiac and respiratory gating techniques which have vastly improved the quality of images of the contents of the thorax.

It is considered that the optimum magnetic resonance imaging system should be based on a well shimmed super-conducting magnet with a field strength of between 0.15 and 0.6 Tesla. It should incorporate well designed receiver coils, a facility to perform cardiac gating and a powerful computer for optimum image processing.

THE GASTROINTESTINAL TRACT—PITFALLS AND PATHOLOGY ENCOUNTERED WITH THE USE OF ULTRASOUND

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Ultrasound is not an imaging technique that is primarily employed in the examination of the stomach and intestines. However, certain segments of gut can be identified from their echographic pattern and anatomic position, and require to be differentiated from other contents of the abdominal and pelvic cavity.

Sonographically, the bowel masquerades as amorphous solid masses, mixed solid and cystic masses, and complex loculated fluid collections. Due to its varied acoustic characteristics, the bowel produces many artefacts and pseudotumours, and these unwanted phenomena can cause confusion in interpretation of the ultrasonic image. Echoes from different segments of gut can vary from highly reflective gas, similar to bone, fibrous tissue, calcification or fat, to viscid or clear fluid filled masses similar in reflectivity to renal parenchyma, muscle, blood, or serous fluids. Pathological lesions may be solid, cystic, or mixed. Interpretation can be difficult and serial observation with real-time scanning is an essential part of the diagnostic procedure as static records are often misleading.

Ultrasound is now employed to assess a widening spectrum of gastrointestinal tract pathology. Useful diagnostic information is obtained in a significant proportion with a definitive diagnosis in a smaller number of cases.

NUCLEAR MAGNETIC RESONANCE IN THE DETECTION, DIAGNOSIS AND STAGING OF HEAD AND NECK CANCER

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Three-hundred and eight patients with diagnosed or suspected extracranial head and neck pathology have been examined on the Aberdeen Mark 2 NMR imager operating at 3.4 MHz, 0.08 Tesla. This represents about 10% of our workload. Of these patients 88 have been examined as part of a comparative imaging trial (NMR vs CT). Radiological examination in these patients has been carefully evaluated and compared with detailed clinical, surgical and pathological examination. In each instance we have attempted to determine how the extra information might change patient management.

Preliminary results show that the much greater soft-tissue contrast seen on NMR images is appreciated by our surgeons. Vascular structures are clearly seen without the use of contrast agents. NMR appears better than CT at detecting and displaying most of the lesions we have encountered. Calculated T1 images and local T1 measurement has not yet proved valuable in the differential diagnosis of different lesions, and NMR may prove to be a sensitive, but non-specific, detector of head and neck pathology. We have not yet found NMR useful in detecting recurrent tumour. Changes in tumour size and T1 have been noted following deep X-ray therapy.

COMPARISON OF ULTRASOUND, COMPUTED TOMOGRAPHY AND NUCLEAR MAGNETIC RESONANCE IN GYNAECOLOGICAL MALIGNANCY

J. F. Calder

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The object of the study was to compare ultrasound (US), computed tomography (CT) and nuclear magnetic resonance (NMR) in the diagnosis of ovarian carcinoma, the follow-up of treated ovarian carcinoma and the staging of endometrial carcinoma. It was hoped that one scanning modality, or a combination of modalities, would allow the "second look" laparotomy to be abandoned in the follow-up of treated ovarian carcinoma.

The results, at this stage in the study, in the three situations, are as follows

Ovarian carcinoma

US, CT and NMR were all accurate in diagnosing ovarian carcinoma. However, in nearly every case, all scans underestimated local or abdominal spread. US is the established method of diagnosing ovarian carcinoma. The other two modalities seldom provided information not shown by US and were sometimes less revealing.

Second-look ovarian carcinoma

When there was no tumour recurrence, all modalities correctly predicted normality. All three scans missed local or metastatic spread in a significant number of cases; however, laparotomy also missed distant metastases in four patients. A combination of staging laparotomy and CT provided most information, with US a little inferior to CT. NMR numbers are smaller but this does not appear to offer significant advantages.

Endometrial carcinoma

NMR was considerably better in demonstrating endometrial carcinoma within an enlarged uterus than were US and CT, however, it was still wrong in 25% of cases, giving both false positive and false negative results.

COMPUTED TOMOGRAPHY OF THE CHEST IN NON-MALIGNANT DISEASE

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The value of computed tomography (CT) in establishing the extent of malignant chest disease, particularly the extent of lymph-node involvement, is confirmed. Computed tomography, however, has a place in diagnosis of non-malignant chest disease. The exact site, size and density of mediastinal masses may give valuable clues to the nature of the pathology present. This information is readily available on CT. Computed tomography is also helpful in the staging of systemic disease involving the lungs. In Aberdeen we have assessed a number of patients with Stage I sarcoid by CT. After this procedure 25% were "up-staged" to Stage II. Chest-wall lesions may be readily assessed by CT, and again density measurement may be helpful in diagnosis.

IMAGING REGIONAL CEREBRAL BLOOD FLOW WITH ^{123}I- AND ^{99}Tc^{m}-LABELLED AGENTS

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The techniques used in nuclear medicine to measure regional cerebral blood flow (RCBF) have, until recently, required specialised instrumentation, and image quality has been poor. Two years ago ^{123}I isopropyl amphetamine (IMP) was shown to be trapped by cerebral tissue to an extent which was dependent upon RCBF. As the distribution of the material was stable for several hours, conventional emission tomography could be carried out.

Unfortunately ^{123}I is quite expensive to produce and is not readily available. Within the last few months, following trials in Aberdeen, a new agent labelled with the commonly available ^{99}Tc^{m} has been identified. This radiopharmaceutical appears to behave in a similar way to IMP.

The two agents have been used to study RCBF in a variety of pathologies. In patients with infarcts, the images showed no uptake in infarcted tissue, but there was also decreased perfusion in adjacent tissue. These latter areas often appeared on NMR. Tumours, like infarcts, also showed no uptake of material. Surprisingly, perhaps, even the so-called vascular tumours had no uptake.

Regional cerebral blood flow patterns in patients diagnosed as having dementia have also been studied. In senile dementia of the Alzheimer type, a characteristic pattern of bilateral reduction in RCBF in the parieto-occipital regions was noted; these areas often appeared normal on NMR. Multi-infarct dementia images appeared to vary from almost normal to images with marked focal defects. Once again not all these defects could be seen with NMR. In cases of both alcohol-related dementia and Huntington's chorea no focal abnormalities were seen.

PHENOL SYMPATHECTOMY

S. Sutton

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This paper presents a retrospective review of 107 patients who underwent chemical sympathectomy under local anaesthetic for the relief of symptoms due to peripheral vascular disease of varying aetiology. All of the patients were considered unsuitable for definitive vascular reconstruction because of cardiac or respiratory problems which precluded general anaesthetic.

Results based on objective observations in follow-up clinics indicate an initial high success rate of 86% of the patients which fell to 60% after an interval of 6 months. The objective and subjective effectiveness of the phenol sympathectomies performed was also assessed after a 12 month interval through the patients' general practitioners. Of the 72 sympathectomies for which information was available from this source, 70% of the patients showed an overall and maintained improvement of their symptoms up to that time, or until their death from an unrelated cause.

Details of the technique of sympathectomy are described with an emphasis on its simplicity and lack of invasiveness, and its suitability to be undertaken in small X-ray departments. Methods whereby the likely effectiveness can be assessed at the time of the sympathectomy are discussed. A small prospective study suggests that the measurement of the rise of skin temperature using a simple thermocouple may provide a useful and simple way of assessing the accuracy of phenol instillation at the time of the procedure.

COMPUTED TOMOGRAPHY OF THE CHEST IN MALIGNANT DISEASE

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In the last 25 years, the incidence of bronchogenic carcinoma in Scotland has risen from 300 per million to 800 per million, and is 60% higher than in England and Wales. Consequently, a diagnostic test which accurately assesses operability status would be advantageous and would allow less inappropriate thoracotomies.

During the last 3 years, all patients under the care of the thoracic surgeons and physicians who were being assessed for thoracotomy, have had a computed tomography (CT) scan of the thorax. Initial results from 185 cases of primary bronchogenic carcinoma show an 80% agreement between CT and operative (including pathological) findings in the 116 patients who had a thoracotomy. The majority of the other 20% of patients had more advanced disease than was suggested by CT. Sixty-nine patients had no thoracotomy, with 31 being "inoperable" on CT alone. The role of CT of the thorax in assessing patients with suspected metastatic disease of the lungs is discussed and examples given. Primary and secondary malignant disease arising in the mediastinum, lung or chest wall is well shown on CT and this allows percutaneous needle biopsy to be performed for histological diagnosis. Computed tomography has added greatly to the non-invasive assessment of thoracic malignancy, providing quickly obtainable and reliable information.

MULTIMODALITY TREATMENT FOR OPERABLE CARCINOMA OF THE OESOPHAGUS

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A prospective non-randomised study to assess the value of combined pre-operative radiotherapy and cytotoxic chemotherapy plus post-operative chemotherapy for operable carcinoma of the middle and lower oesophagus was started at the end of 1975.

Pre-operative radiotherapy (2500 cGy) over 5 days, using a three-field technique in the majority of cases, was combined with chemotherapy varying with cell type and time of entry into study.

Resection was a simple one-stage procedure by left thoracotomy carrying out partial oesophago-cardiectomy with a high anastomosis some 4–8 weeks after chemotherapy and radiotherapy. The pre-operative therapy caused no additional problems and contributed to a high resection rate. There was a relatively low mortality and morbidity, and in a number of cases the tumour, both adeno and squamous, was apparently ablated. Results for 3 and 5 years are presented.

Interestingly, the majority of cases were adenocarcinoma. Previous interim analysis of 107 cases showed disease-free survival after 3 years of 13/70 (19%). The local recurrence was notably low—18/107, and a documented 40% of cases died of distant metastases.

The combination of chemotherapy, radiotherapy and surgery appears beneficial, but a randomised study to evaluate radiotherapy and surgery against chemotherapy and surgery is being undertaken.

In operable cases endoscopic coring out of tumour followed by chemotherapy and radiotherapy allowed patients to swallow, usually until death, and prolonged useful life. It obviated the need for gastrostomy, palliative bypass, or intubation.

CARCINOMA OF THE BREAST—ADJUVANT TAMOXIFEN AND CHEMOTHERAPY

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Tamoxifen is now widely used to treat all stages of breast cancer, and over 50 randomised trials have been commenced world-wide to assess the value of tamoxifen as adjuvant therapy.

Current adjuvant trials fall into three groups:

(a) those in which tamoxifen is the sole form of systemic therapy and is being randomly compared to a control group,
(b) those in which the comparison is of tamoxifen additional to adjuvant chemotherapy versus the same adjuvant chemotherapy alone, and
(c) a few trials in which there is a direct comparison of adjuvant tamoxifen with adjuvant chemotherapy.

A preliminary amalgamation analysis of the early mortality data of 43 trials in the first two groups was carried out in October 1984. This showed a significant overall survival advantage, particularly in women over 50 years of age with node involvement. Even with the large number (over 16 000) available for analysis, there were too few in the younger age group for reliable results. No interaction was demonstrated when chemotherapy was added. This combined analysis was without detail, since only commonly available parameters of numbers dead within two age groups and by clinical node status were submitted.

There remain three major areas of controversy regarding adjuvant tamoxifen, namely:

(a) how long should the therapy last?
(b) who should be selected?
(c) should ER status be considered?

These are common variables found within current trials, the individual results of which are not totally consistent.

ADJUVANT SYSTEMIC CHEMOTHERAPY IN BREAST CANCER

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In the last 10 years a variety of cytotoxic drug regimes and several different forms of hormonal manipulation have been evaluated in the treatment of early breast cancer on the assumption that such methods of treatment might eradicate occult micrometastases which are already present at the time of initial presentation.

Taken overall, the early results were disappointing although Nissen-Meyer using short-course post-operative single agent chemotherapy, and Bonadonna using repeated pulses of combination chemotherapy post-operatively, reported a significant prolongation of both relapse-free survival and overall survival in certain subsets of patients. Most of the studies from the UK, however, have shown no overall benefit.

The potential benefit of adjuvant systemic cytotoxic therapy must be balanced against the side-effects. Nausea, vomiting, mucositis, alopecia and increased psychological morbidity have all been reported. The incidence and severity of these problems will be reduced if the trend towards shorter courses of chemotherapy continues.

While the results of individual trials have until now been disappointing, a recent combined analysis of *all* world-wide trials of adjuvant cytotoxic chemotherapy suggests that chemotherapy will significantly reduce the odds of death in pre-menopausal women by 40% This analysis, however, took no account of duration of treatment or length of follow-up, but suggests that this type of combined analysis will play an increasingly important part in the evaluation of adjuvant systemic chemotherapy.

Book review

Fuch's Principles of Radiographic Exposure, Processing and Quality Control. 3rd edit By Q B Carroll, pp xx+365, 1985, (Charles C. Thomas, Illinois), $29 75

ISBN 0-398-05081-3

This volume undoubtedly contains much useful, practical guidance regarding the consistent achievement of radiographs of good diagnostic quality It includes instructions for experiments intended to demonstrate the effect on the radiograph of changes in the various "exposure factors". Reference is made to an associated laboratory manual and workbook which presumably extend the experimental instructions to the student.

Unfortunately, an unqualified recommendation of the value of the book is not possible. Certainly the use in the title of "Principles of" is misleading and unjustified Early in the text it is stated that "undesirable information that interferes with the subject of interest is referred to as *noise*". There is too much noise in this volume, including many mistakes For example: "reduction is actually chemical oxidation"; "(film) contrast is Density Difference divided by exposure difference" (actually difference in log exposures); "(Radiographic) contrast is Density ratio" (actually density difference); "a 15% kVp leads to a change in density by a factor of 2" (actually a change in mAs by a factor of 2 to maintain constant density), "Compton effect does not contribute to useful contrast" (it does); "doubling the amount of radiation at the film doubles the density" (it does not)

Whilst these errors seem to indicate a lack of understanding, maybe they are not important since they are invariably accompanied by correct practical guidance More objectionable is the attempt to explain everything in words. Too often this leads to a relatively simple situation appearing complex and confused. It is almost unbelievable that a film characteristic curve is not shown or even referred to until p. 341, in spite of the fact that contrast, density, latitude, etc, have all been discussed earlier

In summary this is not a book which will help much with understanding but, if you need to be told how to do the job well, have a good look at a library copy before you buy. In view of the excellent production and large number of photographic illustrations, it is not too expensive.

J B MASSEY

BIR North of England Branch: 1985 Autumn Meeting

The 110th meeting of the North of England Branch of the British Institute of Radiology was held at the Northern General Hospital, Sheffield, on Saturday November 2, 1985, when the following papers were presented

Interventional radiology of the back

H A. Euinton
Northern General Hospital, Sheffield

Sciatic pain due to lumbar nerve-root compression is commonly due to intervertebral disc prolapse in the younger patient. The level of disc prolapse may be determined clinically, but confirmation is usually sought by radiculography or CT. If necessary, further confirmation may be obtained by discometric analysis.

Relief of root compression may be achieved by surgical excision or by the injection of an enzyme to shrink the disc material. The indications for chemonucleolysis are the same as those for elective discectomy.

Above the age of 50 years, entrapment of lumbar roots by bony hypertrophy of the facet joints is the predominant cause of sciatic pain. These patients often have few neurological signs, and clinical prediction of the root level is difficult. Radiculography is less accurate in this condition that in disc prolapse. In a series of 40 patients with bony entrapment shown at operation, we had correctly predicted the involved level in only 20 patients by radiculography and 10 patients had an entirely normal radiculogram.

In an attempt to identify the offending nerve root, we have injected contrast medium into the peri-radicular space of emergent nerve roots through a fine needle. This stimulation of the offending root reproduces the symptomatic pain, thus confirming the pre-operative level prediction. Surgical decompression may then be limited to one root, thus minimising the extent of extradural fibrosis.

Percutaneous laser thermal angioplasty

D. C. Cumberland and D. I Tayler
Northern General Hospital, Sheffield

Laser energy has been shown experimentally to vaporise thrombus and atheroma (Abela et al, 1985), suggesting that it may have a role as an adjunct to percutaneous angioplasty. If more complete occlusions could be traversed, this would increase the proportion of patients to whom angioplasty can be offered, but a reliable means of obtaining a therapeutic effect while avoiding vessel-wall perforation by adjustments in wavelengths or delivery systems has not yet been found.

We have used argon laser energy transmitted down a quartz fibre, passed through a percutaneously introduced Teflon catheter in 15 patients having femoral popliteal angioplasty. Though some luminal improvement was obtained in 10 cases, extravasation indicating wall perforation occurred in two occlusions (without sequelae), despite a known intraluminal fibre position (Cumberland et al, 1986).

Animal work has shown that a metal-tipped laser fibre, or "laser probe", in which the laser energy is converted rapidly to heat, produces a better channel with much less perforation risk than a "bare" laser fibre (Sanborn et al, 1985). We have used this probe in 36 arteries in 34 patients having percutaneous femoral/popliteal angioplasty. Favourable initial experience has enabled us to use it initially to traverse 20 complete occlusions up to 35 cm long (mean 8 cm). A conventional guide wire was initially abutted on to the proximal ends of the occlusions to classify them as either probably "easy" (n = 3) or probably "difficult" (n = 10) to traverse by conventional means. Previous sustained attempts to recanalise some occlusions had failed: these were classified as "impossible". The laser probe successfully traversed all three "easy", nine of 10 "difficult" and five of seven "impossible" occlusions. An adequate channel was thus produced for subsequent guide-wire and balloon-catheter passage.

Thus the laser probe facilitates the crossing of complete occlusions and has successfully traversed some lesions which were impossible by conventional angioplasty technique. This has implications for the treatment of arterial disease.

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Pituitary imaging in the digital era

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Computed tomography of the mediastinum

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Aspects of cholangiography

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The diagnosis of biliary disease still presents a challenge despite the availability of ultrasound and CT. Cholangiography, by whatever method, has still a very important part to play. Changing trends noted in the literature are reflected in our clinical practice in Sheffield, where endoscopic retrograde cholangiography has supplanted percutaneous transhepatic cholangiography in most clinical situations. This has resulted from the obvious advantages of endoscopic retrograde cholangiography not only because it provides information regarding the pancreas but also because of its therapeutic role.

A wide range of presentation of calculous biliary disease was presented, illustrating difficulties in diagnosis, particularly with intrahepatic calculi and with calculi in the cystic-duct remnant. The importance of showing all the biliary tree was emphasised together with the need to obtain radiographs in multiple positions. Non-opacification of any section of the biliary tree should lead to the suspicion of occlusion of the radical supplying that area, and further attempts should be made to show the area in question, either by positioning or by percutaneous needle puncture of that area.

The problem of the diagnosis of suspected benign strictures in the biliary tree remains. Several cases were shown to illustrate the difficulty in diagnosis with multiple intrahepatic strictures on cholangiography, when liver biopsy had excluded malignancy but had been unable to give a precise diagnosis. Without involvement of the extrahepatic biliary tree, a presumptive diagnosis of primary sclerosing cholangitis is difficult to make, and it is likely that this condition has been overdiagnosed in patients with ulcerative colitis, where discrimination between it and other fibrosing liver conditions is very difficult on cholangiography. A number of benign iatrogenic strictures were demonstrated, including examples of choledochojejunostomy and misplacement of the upper limb of a T-tube in the intrahepatic ducts.

It is difficult to discriminate between cholangio-carcinoma and extrinsic compression from malignant lymph nodes at the porta hepatis on cholangiography without the aid of other imaging modalities and aspiration biopsy. The investigation of suspected obstruction in the distal common bile-duct should always be by endoscopic retrograde cholangiography, for vital information about the pancreatic head would thereby be obtained. Strictures in this portion of the biliary tree may be associated with carcinoma of head of pancreas or fibrosis from chronic pancreatitis. With strictures of the distal common bile-duct, the state of the duodenum should always be determined, because evidence of primary or secondary involvement of the duodenum can aid in both diagnosis and prognosis. Many case demonstrations were presented to illustrate these points.

Ultrasound of the hip in infants and children

R J. Peck and G. M. Steiner
Children's Hospital, Sheffield

The hip is proving to be the most accessible joint for ultrasound examination. The "irritable-hip" syndrome in children is a well recognised problem, and ultrasound is a quick non-X-ray method of diagnosing and following-up these children. Effusion in the joint space and occasionally stand-off of the femoral head can be seen. The anatomy and techniques for this procedure were discussed. Ultrasound may also have a role in the diagnosis of congenital

continued opposite

Report of the 1985 Eastbourne meeting of the International Commission on Radiological Protection

The four expert committees of the International Commission on Radiological Protection (ICRP) met in Eastbourne, from October 27 to November 7, 1985. In addition, representatives attended from the Commission of the European Communities, the International Atomic Energy Agency, the International Commission on Radiation Units and Measurements, the International Radiation Protection Association, the OECD Nuclear Energy Agency, the International Commission for Protection against Environmental Mutagens and Carcinogens, the United Nations Scientific Committee on the Effects of Atomic Radiation, the United Nations Environment Programme, the World Health Organisation, and Pergamon Press.

At the meeting, there was a wide-ranging discussion of the programme of work of the Commission and its committees over the next four years. One report, "Data for use in protection against external radiation", was adopted and will be published in the Annals of the ICRP early in 1986. Another report, "The quality factor in radiation protection", produced by a joint ICRP/ICRU task group, giving advice to the two Commissions, was considered, and its publication by ICRU was approved. Other topics on which reports are in an advanced stage of preparation include:

the effects of irradiation on the development of the central nervous system,
the metabolism of plutonium and related elements;
estimation of doses per unit intake for a wide range of radiopharmaceuticals,
lung cancer risks to the general public from inhaled radon daughters.

Other work in hand by the Commission and its committees includes:

a review of RBEs for non-stochastic effects;
development of new models for radionuclide deposition, retention and dosimetry in the lung;
a comprehensive revision of ICRP Reference Manual,
development of recommendations for protection of the patient in nuclear medicine;
production of a report on the application of the Commission's system of dose limitation to medical workers,
a revision of the recommendations concerning monitoring of workers for internal contamination and the interpretation of bioassay data;
a review of various methods of optimisation of protection.

Within the Commission and its committees, preliminary studies are being undertaken relevant to the basic policies of the Commission, as a background for any eventual revision of the Commission's recommendations.

The next meeting of the Commission will be in Vienna April 20–24, 1986.

dislocation of the hip and Perthe's disease. Examples of these conditions were shown.

Investigation of the adult urinary tract: real-time ultrasound, intravenous urography, or both?

B. Jagjivan, D. R Naik and D. J Moore
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Intravenous urography is unpleasant for the patient undergoing the investigation and has a small, but real, risk of serious adverse reaction. There is some confusion over which investigation is most appropriate in patients presenting with urinary symptoms, and, in many cases, this has lead to multiple examinations.

An interim report on 250 cases examined by both ultrasound and intravenous urography (IVU) was presented. The only real "weakness" of renal ultrasound is in the assessment of calculi, in which cases it was shown to be unreliable. The results were reviewed according to the commoner indications for referral. In patients with vague abdominal pain or recurrent urinary-tract infection, ultrasound with a plain abdominal radiograph was shown to be adequate for assessment. The patient with true renal colic should also be assessed initially by ultrasound and a plain abdominal radiograph. Ultrasound demonstrated renal-tract dilatation in all except one case of ureteric calculi. An IVU should be performed if this examination is normal.

Patients presenting with macroscopic haematuria can be initially assessed by ultrasound, when almost all abnormalities will be detected except renal or ureteric calculi, which will require a plain abdominal radiograph. If a mass lesion is seen on ultrasound, then an IVU will demonstrate normality and function of the contralateral kidney, as well as confirming the abnormality. Cystoscopy should not be omitted because neither IVU nor ultrasound can be relied upon to demonstrate small bladder tumours.

Ultrasound examination had the added advantage of showing unsuspected pathology such as ovarian lesions, aneurysm of the abdominal aorta and metastases in the liver.

The results from this study suggest that proper use of ultrasound can replace IVU in the vast majority of cases of suspected urinary-tract disease.

Deep vein thrombosis: do we need venography?

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Correct diagnosis of deep vein thrombosis is essential to prevent the risk of pulmonary embolism or the risk of haemorrhage from anticoagulants if an incorrect diagnosis of deep vein thrombosis is made. Unfortunately, the contrast media used in the standard test for deep vein thrombosis, the X-ray venogram, can also induce venous thrombosis. Even the new low-osmolar contrast media are not entirely risk-free.

Fifty patients were evaluated clinically and examined by Doppler ultrasound, impedance plethysmography and radionuclide venoscan using ^{99}Tc^{m}-labelled fibrinogen for comparison with X-ray venography using Iopamidol 300. A further 88 patients were examined by liquid crystal thermography and compared with X-ray venography. X-ray venography proved to be the most accurate technique, with the clinical examination least accurate. It is suggested that the request rate for X-ray venography could be reduced by 80% if liquid crystal thermography were used as a screening test, followed by a radionuclide venoscan. Of 100 patients presenting with symptoms of deep vein thrombosis, a negative thermogram, which is extremely reliable (one mistake in 88 patients), would exclude 36 patients from further testing. Positive thermograms need to be investigated further with a radionuclide venoscan, whereby a further 43 patients could be confidently diagnosed as positive or negative. The remaining 21 patients would require X-ray venography. This diagnostic approach would reduce morbidity, time and cost. The chance of missing a deep vein thrombosis would then be only 1 25%.

Radon in houses: NRPB surveys

Radon, a naturally occurring radioactive gas, is the most significant source of radiation exposure in the country and there are marked regional variations. These are the conclusions drawn from surveys by the National Radiological Protection Board.

The provisional results were announced in a paper (A D Wrixon, "Human Exposure to Radon Decay Products") presented to the Conference of the National Society for Clean Air at Scarborough on October 17, 1985.

Public concern is most frequently expressed about radioactive discharges from the nuclear industry, yet only 0.1% of the average radiation dose in the UK is due to this practice. Around 90% is caused by natural sources—cosmic rays, gamma rays, radioactivity in diet and radon in air.

Radon gas is created by the trace quantities of uranium in the ground and in building materials. The gas moves through rock and soil or brick and concrete, and enters the atmosphere. Levels in outdoor air are low, but radon accumulates indoors because of restricted ventilation. Radon undergoes decay into solid radioactive products, which attach themselves to dust particles in the air. When these are inhaled, they irradiate the lung.

Provisional results from the national survey show that radon concentrations in London are about half the average value, in eastern England about average, and in southwest England about three times the average. The highest regional levels were found in Cornwall, with typical values around 10 times the national average, and specific values over 10 times higher still. Elevated levels were also found in Devon and in the Pennine region. Contrary to expectation, levels in Aberdeen were below the national average, probably because of the type of granite and local building practices.

There is no direct evidence that exposure to radon decay products in the home causes harm to human beings. There is evidence, however, that the prolonged exposure of uranium miners (and other miners) to high levels of radon decay products underground causes lung cancer. It is, therefore, necessary to make the cautious assumption that there might be a proportionate risk to the public at the levels of indoor exposure found.

For further information, please contact the NRPB Information Office, Abingdon (Tel 0235-831600; Matt Gaines ext. 410, Gill Wilkinson ext 514)

Obituary

Dr Constance A. P. Wood, M.A., D.M.R.E.(Cantab.), M.R.C.S., M.R.C.P.(Lond.), F.F.R.

Dr Constance Wood, who died on October 11 1985 in Hammersmith Hospital, was a distinguished pioneer, as a woman doctor, in the advancement of her specialty – the treatment of cancer by radiotherapy, and as the Director between 1941 and 1962 of the first Medical Research Council Unit in this subject. Her MRC Radiotherapeutic Research Unit was successful in several fields; the design and usage of the teleradium unit (the predecessor of telecobalt units); the then new science of radiation biology; the assessment and introduction of the megavoltage X-ray linear accelerator, now the standard unit for radiotherapy of cancer; the early use of artificial radioactive isotopes; and, above all, the medical use of the cyclotron.

Dr Wood was born in Wolverhampton in 1897 and had two elder brothers and a younger sister. She went to Wolverhampton High School for Girls, after beginning studies at kindergarten, and always respected the principles inculcated there, but only as supplementary to her upbringing by loved and respected parents. She did well at school in languages, swimming and hockey, and became School Captain. She became seriously ill in 1914 when there was one of the first of the world-wide epidemics of influenza. Her mother persuaded the local education authority to allow her to sit the local university scholarship examination at home in bed, and she came first. Her first choice of studies was languages and in July 1914 she was studying with a family in Lille. Rumours of war led to the despatch by her father of one of her elder brothers "with twenty sovereigns" to fetch her home just before the outbreak of World War I, involving long journeys on foot to Ostend to catch the last available cross-Channel steamer. The war had other consequences. Dr Wood's eldest brother was severely wounded in France in 1916. He recovered but was unable to continue with his intended career in medicine, much to his father's regret, and therefore his sister, Constance, decided that she would study medicine. After preliminary work in Birmingham University she went to Newnham College, Cambridge, 1917–20, to take the Natural Sciences Tripos, and then studied clinical medicine at King's College Hospital Medical School, London, one of the first three women students at King's, where many of the men would have preferred "a good rugger player". There were stories at the time of one of the surgeons giving a legacy to King's on condition that there were no more women students, only to be counterbalanced by another gift from a wealthy lady on condition that the women stayed!

Dr Wood was appointed resident radiologist at King's between 1923 and 1926, taking up the new specialty of radiotherapy, going on subsequently to work at the then Royal Cancer Hospital in Fulham Road, after obtaining the Cambridge Diploma in Radiology and Electrology. She visited many other centres at her own expense, in Paris, Stockholm, the USA, and elsewhere. She began to observe and study patients treated by X-ray therapy and radium carefully and meticulously, and was recommended to Sir Walter Fletcher of the MRC for a research post. "Large quantities" of radium (*i.e.* a few grams rather than milligrams) had become available in London in the early 1920s and its initial successes in treatment of cancer, in Stockholm and Paris especially, led to the formation of "The Radium Beam Therapy Research Unit". This was set up with 8¾ grams of radium from the Belgian Congo, at the London Radium Institute under a research team directed by Dr Wood, appointed jointly by the medical Royal Colleges and the British Empire Cancer Campaign as well as the MRC. The first four years, 1934–1938, led to the development of methods of dosage and equipment and to some success in treatment of cancers of mouth, tongue, pharynx and larynx. By 1938 it had even become possible to discuss the usage of neutrons and radioactive nuclides from a cyclotron (developed by Lawrence at Berkeley, California). At the outbreak of World War II, work with radium became restricted and the radium itself was placed underground in 50 feet boreholes. In 1941 the MRC took full control of the research and re-established the Unit under Dr Wood's direction at the new Postgraduate Medical School at Hammersmith Hospital.

Much very good and careful work followed. The wartime clinical research was described in absorbing detail in the MRC Special Report published later by Wood and Boag in 1950. It was a

model description of this kind of study, with elaborate detail of the clinical findings, photographic records, and with the physical aspects of the treatment. The major findings were not only that this kind of radiation treatment was of value for oral cancer, but that the high energy γ rays of radium did not have any peculiar biological advantage over other ionising radiation. Work had continued during the bombing of London, so that random allocation of treatment was not practicable because the 250 keV "high energy" X-ray unit could not always be kept operational, and the radium had to be sent underground when there was heavy bombing.

During the war, radar had been developed and the magnetron designed for this was used in the new megavoltage X-ray linear accelerator built for Dr Wood's unit, at the instigation of the MRC, at the Radar Establishment at Malvern, just after the war. It was also decided by the Council that a cyclotron should be constructed at the Hammersmith, the only cyclotron at a hospital and devoted exclusively to medical research for the next 25 years. The cyclotron was inaugurated by the Queen in 1955, two years after the first patient had been treated on the linear accelerator. Other developments at the Hammersmith under Dr Wood included early work with artificial radioactive phosphorus and iodine, research into positron emitting nuclides produced in the cyclotron, and much of the classic early work in radiation biology. There are too many well known living radiation research workers to mention any by name except for L.H. Gray, who was appointed in 1946 as deputy director and became one of the main fathers of modern radiation biology. He left Hammersmith in 1953, much to Dr Wood's regret, but the work he began there continued. By the time Constance Wood retired in 1962, radiotherapy with high energy electrons and 8 MeV X rays was routine. Fast neutron therapy of patients had not yet begun, but the essential pre-therapeutic research on the skin of the pig was well under way Dr Wood had also played her part not only in the demonstration that radiotherapy was a worthwhile treatment for cancer, but that its practitioners could care for patients in their own right, needed hospital beds of their own, and should take over X-ray therapy from their diagnostic colleagues, and radium work from the surgeons and gynaecologists

Dr Wood's main personal publications were almost certainly the two MRC Special Reports No 231 in 1938 and No. 267 in 1950, written with colleagues, but clearly conveying her own early attention to detailed observation Much of the later work in her unit was well described in *Modern Trends in Radiotherapy* edited by Tom Deeley with her and published in 1967.

Dr Wood loved the hills and open air, especially near her wartime family home at Faintree in Shropshire, and used to enjoy driving there from London in an open car. She particularly liked to spend time on purchasing antiques to be cherished in her final flat in Campden Hill Court She was kind and helpful to radiographers as well as to medical and scientific colleagues and certainly underestimated her own achievements. Her department was her main interest, but of course she was an active Fellow of the Faculty of Radiologists, predecessor of the present Royal College, and was elected Vice-President for 1956–7. Her later years were troubled by illness but she still enjoyed attending meetings of the College, and was particularly pleased to be able to come to the Jubilee meeting of her old department as guest of honour only a few months before her death She had achieved very much.

Keith E Halnan

BIR Calendar Events

Unless otherwise indicated, enquiries about the following events should be addressed to the Assistant Secretary, Programme, British Institute of Radiology, 36 Portland Place, London W1N 3DG (Tel 01-580 4085)
The meetings are at 36 Portland Place unless otherwise stated.
Attendance is open to non-members

Abdominal Sepsis
March 26, 1986
Including special lecture by Dr P. C. Freeny.
Joint RSM/RCR/BIR all-day meeting organised by RSM and held at the RSM.

Radiology '86
April 9–11, 1986
Bristol
44th Annual Congress and Exhibition

Incorporating the joint spring meeting of the Institute with the Royal College of Radiologists and the Section of Radiology of the Royal Society of Medicine. It will be held in the picturesque setting of the Bristol waterfront

The scientific programme (CME accredited) will encourage discussion of contemporary aspects of the radiological sciences and will include

BIR Mackenzie Davidson Memorial Lecture (Dr A. Margulis: "The Impact of New Imaging Technology on Health Care, Research and Teaching")
BIR Mayneord Lecture, sponsored by 3M UK Plc (Mr G Higson· "Seeing Things More Clearly")
RCR George Simon Lecture (Professor N. M. Bleehen· "Raleigh's Revenge")
All-day Seminar—Buying for Radiology organised with the Association of National Health Service Supplies Officers
All-day Seminar—Biological Basis of Radiological Protection and its Application to Risk Assessment
Proffered Papers
Large Technical and Scientific Exhibition
Annual Dinner, April 10

Annual Dinner
April 10, 1986
Holiday Inn, Bristol

Annual General Meeting of the BIR
May 14, 1986
Members only.

Safety of Diagnostic Ultrasound and Presidential address
May 15, 1986
Middlesex Hospital Medical School, London W1
Includes the Presidential Address to be given by Dr P. N T. Wells, "The prudent use of diagnostic ultrasound"
Joint BIR/BMUSCOR/IPSM/RCOG/RCR meeting.

Progress in Tumour Radiobiology
May 16, 1986 at 11 00 am
Organised by the Radiobiology Committee (proffered papers).

The Assurance of Quality in Medical Imaging
May 21, 1986
Middlesex Hospital Medical School
All-day meeting organised by the BIR Quality Assurance Working Party in conjunction with Industry Committee.

Conversazione
June 19, 1986 at 7.00 pm
Royal Society of Medicine, London W1
Incorporating the Silvanus Thompson Memorial Lecture: "Seeing through illusion", by Professor R. L. Gregory

Joint RCR/BIR/RSM Autumn Provincial Meeting; RCR Annual General Meeting
September 11–13, 1986
University of Sheffield
Organised by the RCR. Further details from the Meetings Secretary, The Royal College of Radiologists, 38 Portland Place, London W1N 3PG (Tel. 01-636 4432/3).

Library news

The BIR Library is open weekdays 9am–5pm

The Librarian, Mrs Gunnel Ingham, is in attendance Tuesdays and Thursdays 11am–4pm, Mrs Diana Jasper, daily 10am–5pm.

The journal stock includes more than 100 titles Though journals may not be taken out of the library, there is a photocopy service, also available by post.

Most books (excepting the historical collection) are available on loan.

Further information. telephone 01-580 4085

Current journals held in the BIR Library

Acta Radiologica—Diagnosis
Acta Radiologica—Oncology
American Journal of Neuroradiology
American Journal of Roentgenology
Annales de Radiologie
Annals of the ICRP
Applied Health Physics, Abstracts and Notes
Astro Newsletter
Australasian Radiology
British Journal of Cancer
British Journal of Radiology
British Medical Bulletin
British Medical Journal
British Society of Dental and Maxillofacial Radiology Newsletter
Cancer
Cancer Research
Cancer Research Campaign Annual Report
Cancer Treatment Reviews
Cardiovascular and Interventional Radiology
Cell and Tissue Kinetics
Chinese Journal of Nuclear Medicine
Chinese Journal of Radiology
Clinical Nuclear Medicine
(Clinical Oncology. cont as European Journal of Surgical Oncology)
Clinical Physics and Physiological Measurements
Clinical Radiology
Computerized Radiology
Critical Reviews in Diagnostic Imaging
Current Contents (Life Sciences)
Current Opinion in Gastroenterology
Current Problems in Diagnostic Radiology
Deutsche Roentgengesellschaft Informationen
Diagnostic Imaging (USA)
European Journal of Cancer and Clinical Oncology
European Journal of Nuclear Medicine
European Journal of Radiology
European Journal of Surgical Oncology
Excerpta Medica. 14 Radiology
Excerpta Medica. 23 Nuclear Medicine
Fortschritte auf dem Gebiete der Roentgenstrahlen
Gastrointestinal Radiology
Health Physics
Indian Journal of Cancer
Indian Journal of Radiology
International Agency for Research on Cancer. Annual Report
International Atomic Energy Agency Bulletin
International Journal of Applied Radiation and Isotopes
International Journal of Hyperthermia
International Journal of Nuclear Medicine & Biology
International Journal of Radiation Biology
International Journal of Radiation Oncology Biology Physics
Investigative Radiology
Japanese Journal of Nuclear Medicine
Journal Belge de Radiologie
Journal de Radiologie (France)
Journal Européen de Radiothérapie
Journal of Clinical Oncology
Journal of Clinical Ultrasound
Journal of Computed Tomography
Journal of Computer Assisted Tomography
Journal of Nuclear Medicine
Journal of the Canadian Association of Radiologists
Journal of The National Cancer Institute
Journal of The Royal Society of Medicine
Journal of The Society for Radiological Protection
Journal of X-ray Technology
Lancet
Magnetic Resonance in Medicine
Medical Physics
Medical Radiography and Photography
Medicamundi
Meditsinskaya Radiologiya (USSR)
Meetings on Atomic Energy
Neuroradiology
Nuclear Medicine Communications
Oncologia (Rumania)
Pediatric Radiology
Physics in Medicine and Biology
Proceedings of The American Association for Cancer Research
Proceedings of the American Society of Clinical Oncology
Rad
Radiation Protection Dosimetry
Radiation Research
Radiographics
Radiography
Radiography News
Radiologia Medica (Italy)
Radiologic Clinics of North America
Radiological Protection Bulletin
Radiology
Radiology Japan
Radiology Now
Rays
Rivista di Radiologia (Italy)
Seminars in Nuclear Medicine
Seminars in Roentgenology
Seminars in Ultrasound
Skeletal Radiology
Strahlentherapie
Ultrasonic Imaging
Ultrasonics
Ultrasound in Medicine and Biology
Urologic Radiology
World Health
Yearbook of Diagnostic Radiology

Recent additions to the Library

BSI: BS 4727: Part 5: Radiology and radiological physics terminology. 1985
BSI. BS 6641. Glossary of medical terms. 1985
Collins pocket English dictionary. 1985
Dobbs, J. & Barrett, A: Practical radiotherapy planning 1985
HMSO. The protection of persons against ionising radiation arising from any work activity. Approved code of practice. 1985
IAEA. Assessment of radioactive contamination in man Proceedings of an international symposium in Paris, November 1984.
IAEA: Radiopharmaceuticals and labelled compounds. Proceedings of an international conference in Tokyo, October 1984.
Seeram, E.. X-ray imaging equipment. 1985
Williams, E. D (Ed.). An introduction to emission computed tomography 1985

Meetings, Courses, Notices

As a service to our readers, the title, date and place of meetings and contact address will be inserted free of charge: any additional information will be charged at £1.75 per printed line, per insertion. Please contact the Managing Editor.

Combined Course in Clinical Oncology and Radiotherapeutics
March 17–21, 1986
The Postgraduate Medical Centre, Lancaster House, Glasgow
Further details and application forms Dean of Postgraduate Medicine, University of Glasgow, Glasgow, G12 8QQ (Tel. 041-339 8855, ext 7274)

Obstetric and Neonatal Blood Flow
April 8–9, 1986
King's College Hospital, London
Further details: Biological Engineering Society, Royal College of surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN (Tel 01-242 7750)

The Actinides
April 9, 1986
City Conference Centre, 76 Mark Lane, London EC3
This meeting is organised by the Society for Radiological Protection and will be followed by the Society's Annual General Meeting.
Further details Programme Committee Secretary, Professor J H. Martin, Department of Medical Biophysics, Building 15, Park Wynd, University of Dundee, Dundee DD1 4HN.

Symposium on Malignant Disease and the Skin
Departments of Dermatology and Radiation Oncology
April 11–12, 1986
University of Liverpool
Subjects include epidemiology, pathogenesis and therapy
Speakers include Prof J. A A. Hunter, Edinburgh, Dr John White, Southampton, Dr Neil Smith, London, Prof Wilson-Jones, London, Dr A Chu, London, Dr S. S Bleehen, Sheffield, Dr Margaret Spittle, London. Accommodation:University Hall of Residence. Registration fee. £25.00
Further details. Prof. C F H. Vickers, Department of Dermatology, Royal Liverpool Hospital, or Dr M. J. Garrett, Department of Radiation Oncology, Clatterbridge Hospital, Bebington, Wirral

British Nuclear Medicine Society Annual Congress
April 13–16, 1986
at Imperial College, London SW7
Further details. Mrs A. Taylor, BNMS, Conference Secretary, 22 Leinster Avenue, East Sheen, London S14 7JP

Biological and Therapeutic Aspects of Cancer Metastasis
April 14–17, 1986
Vitoria, Spain
The University of the Basque Country (Northern Spain) is organising an International Conference on the "Biological and Therapeutic Aspects of Cancer Metastasis". Topics include immunological and therapeutic aspects in cancer metastasis, host factors in metastasis, organ specificity, genetic heterogeneity of tumour cells, phenotypic heterogeneity of tumour cells, cell membranes and tumour cell-connective tissue interactions Guest speakers include E. Barberá, R. Feldman, I. Fidler, R. Kefford, R Kerbel, L. Olsson, G. Poste, M F. Poupon, V. Schirrmacher and D. Tarin.
Further details. Conference Secretariat, Apartado 1299, 48080 Bilbao, Spain

Images of Living Brain Chemistry: Neuroreceptors
April 18–19, 1986
Baltimore, Maryland
Further details: Diane Heydinger, Program Coordinator, Turner 22, 720 Rutland Avenue, Baltimore, MD 21205, USA (Tel. 301-955 6046).

The National Institutes of Health Consensus Development Conference on Neurological Applications of Positron Emission Tomography
April 21–23, 1986
Clinical Center of the National Institutes of Health, Bethesda, Maryland
Further details: Shelley Clark (Tel. 301-468 6555).

Course on Cancer Epidemiology
April 28–May 9, 1986
Holzhau, East Germany
Further details The Research Training and Liaison Unit, International Agency for Research on Cancer, 150, cours Albert Thomas, 69372 Lyon Cedex 08, France.

1st International Conference on the Clinical Application of Photosensitization for Diagnosis and Treatment
April 30–May 2, 1986
Tokyo
Topics will include tumour localisation and treatment in cancer of various organs, including combined treatment with other modalities
Further details. Dr Yoshihiro Hayata, Tokyo Medical College Hospital, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan.

International Continuing Medical Education Series
Controversies in Medicine
April 30–May 15, 1986
Paris/Versailles, France

August 14–29, 1986
London, England

Update on Laser Therapy
June 25–July 10, 1986
Heidelberg, Germany

Further details: Dr Barry M. Manuel, Department of CME, Boston University School of Medicine, 80 E. Concord Street, Boston, MA 02118, USA (Tel. 617-638 4605)

Sixth International Symposium: Radionuclides and Nephro-Urology
May 5–7, 1986
Hotel Beau Rivage, Lausanne, Switzerland
Further details. A Bischof-Delaloye, Division Autonome de Médecine Nucléaire, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne, Switzerland, (Tel. (021) 41 42 48)

IV Symposium on the Medical Applications of Cyclotrons
May 28–31, 1986
Turku, Finland
Further details. Scientific Secretary, Robert Paul, Turku Medical Cyclotron Project, University Hospital, SF-20520, Turku, Finland (Tel (21) 611 611)

Radiology of the Small Intestine
May 31, 1986
John Radcliffe Hospital, Oxford
Fee £30.00
Particular emphasis will be placed on the small bowel enema technique.
Further details: Dr D. J. Nolan, Department of Radiology, John Radcliffe Hospital, Oxford OX3 9DU (Tel. 0865-817238)

European Gamma-11 Users Meeting
June 4–6, 1986
Guy's Hospital, London
Further details E D. Williams, Medical Physics Department, Sunderland District General Hospital, Sunderland SR4 7TP.

Cardiovascular Radiology and Musculoskeletal Radiology
June 12–15, 1986
Salzburg, Austria
Further details. Dr K. H. Barth, Department of Radiology, Georgetown University Hospital, Washington, DC 20007, USA (Tel. 202-625 2891).

Cambridge Meeting on Chest Disease
July 3–5, 1986
King's College, Cambridge
This residential meeting should be of interest to Consultants and experienced Senior Registrars The format will be as in previous years and the numbers will be limited.
Further details. Dr C D. R. Flower, Department of Radiology, Addenbrooke's Hospital, Hills Road, Cambridge

The Leeds Gastroenterology Course for Radiologists

July 7–11, 1986
St James's University Hospital, Leeds
Further details. Mr Frank Moran, Senior Administrative Assistant, Postgraduate Dean's Office, Leeds General Infirmary, Leeds LS1 3EX (Tel. 0532-432 799, ext. 3631).

Nato Advanced Study Institute on: Physics and Technology of Hyperthermia

July 26–August 9, 1986
Urbino, Italy
Further details: Dr S. B Field, MRC Cyclotron Unit, Hammersmith Hospital, Ducane Road, London W12 0HS

Computers for the Practising Physician: Update 1986

July 27–30, 1986, New Seabury, Cape Cod, Massachusetts
Further Details. Department of CME, Boston University School of Medicine, 80 East Concord Street, Boston, MA 02118, USA

Radiation Oncology Physics 1986

July 27–August 1, 1986
Miami University, Oxford, Ohio
Further details Dr P. A Feller, Oncology Center, The Jewish Hospital, Cincinnati, Ohio 45229, USA (Tel. 513-569 2285).

4th International Congress on Interventional Ultrasound.

August 19–22, 1986
Copenhagen, Denmark
Further details: Spadille Congress Service, DK-3100 Hornbaek, Denmark

International Symposium on Radiotherapy in Developing Countries: present status and future trends

September 1–5, 1986
Vienna
To be convened by the International Atomic Energy Agency Papers to be submitted by February 14, 1986
Further details: M Pankhurst, Atomic Energy Division, Department of Energy, Thames House South, Millbank, London SW1P 4QJ (Tel 01-211 6850)

8th International Radiology Congress: Radiology in Salzburg

September 7–13, 1986
Salzburg, Austria
Further details: Dr D Beatty Crawford, Department of Radiology, University of Connecticut Health Center, Farmington, CT 06032 USA (Tel 203-674 3322)

Paediatric Radiology Course

September 8–10, 1986
Sheffield

Basic paediatric imaging for consultants and senior registrars to enable them to face problems in the DGH and FRCR.
Further details: Dr G. M. Steiner, X-ray Department, Sheffield Childrens Hospital, Western Bank, Sheffield S10 2TH (Tel 0742-71111).

4th Midlands Course in Otoradiology

September 12–13, 1986
Coventry
A comprehensive course in imaging of the petrous temporal bone and associated structures.

This is a course with practical instruction and discussions covering a wide range of investigations suitable for ENT surgeons and head and neck radiologists. Guest lecturers will include Dr Hermann Wilbrand of Uppsala, Sweden and Dr Glyn Lloyd of London.

Further details: Miss M Adams Centre Administrator, Warwickshire Postgraduate Medical Centre, Stoney Stanton Road, Coventry CV1 4FG

4th International Selectron Users Meeting

September 14–17, 1986
British Columbia, Canada
Further details. Dr S M Jackson, Cancer Control Agency of BC, 600 West 10th Avenue, Vancouver, BC, Canada V5Z 4E6

Blood Flow in the Brain

September 23–25, 1986
Strathclyde University, Glasgow
Further details Biological Engineering Society, Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN (Tel 01-242 7750).

Conference on the Interaction of Radiation Therapy and Chemotherapy

September 28–October 1, 1986
The Fort Magruder Inn, Williamsburg, Virginia
Further details Ms Suzanne Bohn, American College of Radiology, 925 Chestnut Street, Philadelphia, PA 19107 USA (Tel. 215-574 3181)

International Conference on Prostaglandin and Lipid Metabolism in Radiation Injury

October 1–3, 1986
Washington D.C.
Further details Dr Thomas L Walden, Biochemistry Department, Armed Forces Radiobiology Research Institute, Bethesda, Maryland 20814-5145 USA

AER Symposium 1986 Tumours and Imaging

October 1–4, 1986
Vienna Hilton Hotel, Austria
Congress President Prof. H Pokieser, c/o Wiener Medizinische Akademie, Alser Strasse 4, A-1090 Wien, Austria (Tel 222-421 383).

Radiology Update

November 7–8, 1986
Cape Town, South Africa
Further details: Prof. B. J. Cremin or Mrs Elliot, Postgraduate Medical Centre, UCT Medical School, Observatory 7925, Cape Town, South Africa (Tel 021-47 1250)

Age-Related Factors in Radionuclide Metabolism and Dosimetry

November 26–28, 1986
Angers
Further details. Dr G. B. Gerber, Commission of the European Communities, DG XII/F1, Rue de la Loi 200, B-1049 Brussels, Belgium (Tel. 02-235 4041).

Asian Regional Conference of The International Organisation for Medical Physics

December 8–12, 1986
Bombay, India
Further details Organising Secretary. Asian Regional Conference on Medical Physics 1986, Association of Medical Physicists of India Division of Radiological Protection, Bhaba Atomic Research Centre, Bombay 400 085, India.

VI Congress of the European Association of Radiology (ECR '87)

May 31–June 6, 1987
Lisbon, Portugal
Further details: Secretariat ECR '87, SPRMN, Av. Elias Garcia, 123–7° DTo, 1000 Lisboa, Portugal, (Tel: 77–05 30), Telex 62074 SPRMN P

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British Journal of Radiology Supplement 19

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Proceedings of a Workshop held at Saclay, France, on October 9–11, 1985, organised by the Commission of the European Communities and the Commissariat à l'Energie Atomique de Protection et de Sûreté Nucléaire, Fontenay-aux-Roses, France.

Skin and underlying tissues are frequently critical structures in radiological protection. Over exposure to ionising radiation can cause serious long-term suffering and disability.

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This Workshop and Proceedings bring together those at the forefront of research in these areas from all over the world. They review the present state of knowledge and attempt to identify specific problem areas which may lead to recommendations for the improvement of radiological protection and for the better management of radiation accidents.

Radiation Damage to Skin is, therefore, a vital reference work for everyone working in radiation protection and dosimetry.

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ISSN 0007-1285
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British Journal of Radiology
Supplement 17

Intended as a standard reference work on the subject, this replaces BJR Supplement 11, published in 1972, and contains typical values for all the types of radiation in common use today Each chapter has been revised and updated wherever new data have become available: the principal extensions cover larger field sizes and longer SSDs for cobalt 60 gamma rays and megavoltage X rays, together with a wider coverage of megavoltage X rays, electrons and fast neutrons

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AUSTRALIA

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The appointee will be responsible for the operation of the Nuclear Medicine Department which currently carries out a wide range of diagnostic and therapeutic tests including diagnostic ultrasound. The Department is well equipped and is located in a spacious, modern section of the hospital. There is a staff of six (6) technologists, nursing and secretarial support.

The appointee will be a member of the Senior Medical Staff of the hospital. This is a Class IV appointment and will be, in the first instance, for a period of 3 years.

The conditions of appointment are as set out in the Hospitals Remuneration Tribunal Determination for Senior Medical Officers and includes five weeks annual leave, cumulative sick leave, two weeks conference leave/year and sabbatical leave entitlement after six years of continuous service.

Superannuation benefits are available. The current salary is Aust.$63567 p.a., plus 10% on-call allowance.

The Right of Private Practice, up to a maximum of 25% of salary, may be granted to the appointee in accordance with the directions of the Health Department, Victoria.

A Memorandum of Information relating to this position is available for intending applicants, and further information may be obtained from the Medical Superintendent, Dr J. J. Griffin, on telephone no. 6134182211, ext. 2009.

Application forms are available from the office of the undersigned, with whom they are to be lodged by the 28th March 1986.

J.F. Pruscino
CHIEF EXECUTIVE OFFICER

RADIATION ONCOLOGISTS

TOM BAKER CANCER CENTRE

The Tom Baker Cancer Centre, serving southern Alberta, opened its new facility in October 1981. The Department of Radiation Oncology has openings for qualified Radiation Oncologists interested in helping development of a rapidly expanding programme. The Department is currently staffed with six radiation oncologists, backed by an active Medical Physics Department, Treatment Planning Unit, Simulator Suite and a full complement of technologists.

Treatment units consist of three linear accelerators, three cobalt 60 units, deep and superficial orthovoltage machines, and a Selectron afterloading unit. A superficial hyperthermia unit has recently been added. Current annual treatment load is approximately 2000 patient courses. Medical physics staff, two simulators, a planning department with VAX and PC12 computers and a mould room facility provide technical support. In addition, there is a departmental nursing staff.

Teaching and research activities are coordinated by university affiliation and cross appointment. The Centre has Departments of Medical, Gynaecologic and Surgical Oncology, Nursing, Psychosocial Support, Palliative Care and major participation by consultant physicians from the community.

Interested candidates should contact:

Dr Keith Arthur, Director
Department of Radiation
Oncology
Tom Baker Cancer Centre
1331–29 Street, NW
Calgary, Alberta
Canada T4N 4N2

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AUSTRALIA

Applications are invited from legally qualified Medical Practitioners for the whole-time position of:

DEPUTY DIRECTOR OF RADIOLOGY

This whole-time appointment will, in the first instance, be for a period of three (3) years, and the appointee will be eligible for re-appointment.

This position is a Class III appointment for which the present salary is Aust.$61 020 p.a., plus 10% on-call allowance, and the conditions of appointment will be in accordance with the Hospitals Remuneration Tribunal Determination for Senior Medical Staff.

The appointee may be granted the Right of Private Practice up to a maximum of 25% of salary, in accordance with the directions of the Health Department, Victoria.

A Memorandum of Information is available for intending applicants, and further information may be obtained from the Medical Superintendent, Dr J. J. Griffin, on telephone no. 61 3 4182211, ext. 2009.

Application forms are available from the office of the undersigned, with whom they are to be lodged by the 28th March 1986.

J.F. Pruscino
CHIEF EXECUTIVE OFFICER

RADIATION ONCOLOGIST

Two posts for Staff Radiation Oncologists (one new, one due to retirement) are available at The London Regional Cancer Centre, London, Ontario, Canada. This is a multidisciplinary cancer centre which is involved in supplying clinical services to a large area of Southwestern Ontario (catchment population is 1.6 million) and sees some 2600 patients in its clinics per annum.

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British Journal of Radiology Supplement 16, 1981

This is a revised version of a working-party report which was first published in 1976 as BIR Special Report 10, and owing to heavy demand has been out of print for some time. The authors consider the place of planning simulators in modern radiotherapy and endeavour to set up guide lines for their future development, covering both specifications for the instruments and the ways in which they are used. The report also discusses the relationship between simulators and transverse axial computed tomography.

The report has been fully updated and is highly detailed, containing 31 pages, 10 figures, and 59 references covering the period 1952 to 1981. The Convenor of the Working Party was C. K. Bomford and other members were Miss L. M. Craig, F. A. Hanna, G. S. Innes, S. C. Lillicrap and the late R. L. Morgan, with G. R. Higson as DHSS Observer.

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The third Mayneord Lecture entitled **Seeing things more clearly** will be given by Mr G. R. Higson BSc, FInstP, CEng, FIEE, Director, Scientific and Technical Services, Department of Health and Social Security. It will be given at the Unicorn Hotel, Bristol, on Wednesday 9th April 1986 at 5 00 pm during the BIR Annual Congress RADIOLOGY '86.

Criteria and Methods for Quality Assurance in Medical X-ray Diagnosis

Proceedings of a Scientific Seminar organised by the Commission of the European Communities and the Centro di Ricerca Applicata e Documentazione, held in Udine, Italy, 17–19 April 1984

British Journal of Radiology Supplement 18

The contributors to this Seminar came from 15 European countries, the USA and Canada. All aspects of Quality Assurance were discussed: the concepts and implementation of QA, the involvement of research, professionals, industry and governments, and the technical aspects of equipment testing, image quality, information content and dose- and cost-reduction.

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(continued from outside back cover) *Page*

Correspondence

Rationale for lung ventilation imaging 297
P. S. Cosgriff and J. M. Berry

Reply
M. J. Nimmo, M. V. Merrick and A. M. Millar

Economics of xenon 127, xenon 133 and krypton 81m for routine ventilation imaging of the lungs 298
J. P. Lavender and J. P. Finn

Reply
M. J. Nimmo, M. V. Merrick and A. M. Millar

Glutathione depletion: does it influence radiosensitisation by misonidazole? 299
O. C. A. Scott

Reply
J. M. Brown and E. A. Bump

Inadvertent buckling of caesium-137 needles—a cautionary tale 302
L. A. Mackenzie

Proceedings of The British Institute of Radiology

Joint Autumn Meeting with the Royal College of Radiologists, Royal Society of Medicine (Section of Radiology) and the Scottish Radiological Society. September 27–28, 1985 303

Book reviews

Skeletal radiography. *S. Bull* 216
A practical approach to modern imaging equipment, 2nd edit. *T. T. Thompson* (Ed.) 216
Differential diagnosis in conventional radiology. *F. A. Burgener and M. Cormano* 224
Radiological anatomy, physics and techniques. Multiple choice tutor. *A. Coral and A. T. Irvine* 230
Radiology of liver circulation. *C. L'Hermine* 240
Iatrogenic disorders of the fetus, infant and child. *G. Kassner* 250
Galliumszintigraphie. *H. Botsch* 250
Radiation Protection (protocol for X-ray dosimetry EULEP). *J. Zoetelief, J. J. Broerse and R. W. Davies* 262
Atlas of roentgenographic measurement, 5th edit. *T. E. Keats and L. B. Lusted* 286
Encyclopedia of medical radiology, Vol. 20. Radiation exposure and radiation protection. *F. Heuck and E. Scherer* 286
Manual of radiographic interpretation for general practitioners. *P. E. S. Palmer, W. P. Cockshott, V. Hegedüs and E. Samuel* 296
Double-contrast radiology of the oesophagus. *G. Rossetti* 296
Fuch's principles of radiographic exposure, processing and quality assurance, 3rd edit. *Q. B. Carroll* 308

BIR Bulletin and Calendar Events *facing page* 308

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VOL 59 NO 699 MARCH 1986

The British Journal of Radiology

Contents

Page

Cartilage-cell-containing tumours of the pelvis: a radiological review of 40 patients 197
G. Buirski, A. H. C. Ratliff and I. Watt

Arthrosonography of the irritable hip in childhood: a review of 1 year's experience 205
R. Adam, G. M. A. Hendry, J. Moss, S. R. Wild and I. Gillespie

The fractional distribution of the cardiac output in man using microspheres labelled with technetium 99m 209
P. A. Crean, T. Pratt, G. J. Davies, M. Myers, P. Lavender and A. Maseri

Persistent sciatic artery. Report of three cases and literature review 217
M. P. Freeman, J. Tisnado and S.-R. Cho

Renal artery stenosis: duplex Doppler evaluation 225
P. A. Dubbins

Renal carcinoma: duplex Doppler evaluation 231
P. A. Dubbins and I. Wells

The mammographic breast pattern and oral contraception 237
S. J. Leinster and G. H. Whitehouse

Intravenous digital subtraction arteriography: a comparison of peripheral versus central contrast injection 241
M. Lea Thomas and P. S. Treweeke

A detailed study of radiation dose and radiographic technique during chest radiography 245
K. Faulkner, M. D. H. Gordon and J. Miller

Radiation therapy of squamous carcinoma of the tonsil: an analysis of prognostic factors and of treatment failures 251
M. P. Vallis, J. Cleeland, P. J. Bradley and D. A. L. Morgan

Dose–response relationships for photodynamic injury to murine skin 257
J. V. Moore, J. P. Keene and E. J. Land

Tumour uptake of radiolabelled pyrimidine bases and pyrimidine nucleosides in animal models IX. Radiolabelled 1-(2′-fluoro-2′-deoxy-β-*D*-ribofuranosyl)uracil and 1-(2′-chloro-2′-deoxy-β-*D*-ribofuranosyl)uracil 263
D. N. Abrams, Y. W. Lee, J. R. Mercer, E. E. Knaus and L. I. Wiebe

Technical notes

The effect of temperature on ultrasonic images in infant cadavers 271
A. C. Lamont and B. J. Cremin

Development and assessment of an image intensifier for real-time X-ray microscopy 273
R. Ll. Davies, N. A. Flores and K. T. Evans

Case reports

Gigantiform cementoma—an unusual incidental finding 277
A. J. Lyons and A. V. Babajews

Duodenal haematoma mimicking traumatic pancreatic pseudocyst 279
N. Raby and H. Meire

Takayasu's arteritis: decrease in aortic wall thickening following steroid therapy, documented by CT 281
K. Hayashi, T. Fukushima, N. Matsunaga and Z. Hombo

Unusual ultrasound appearance of the spleen—a case of hereditary spherocytosis 284
R. Gupta and C. H. Woodham

Case of the month

The case of the missing sign 287
G. Wagener, M. Sandler and F. S. Hough

Short communications

Three-dimensional anatomical images from computed tomographic scans 289
J. E. Gillespie and I. Isherwood

Ultrasound of the painful hip in children 293
R. J. Peck

Patients' complaints after barium enema 294
J. G. B. Russell

(continued on inside back cover)

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Volume 59 Number 70
April 198

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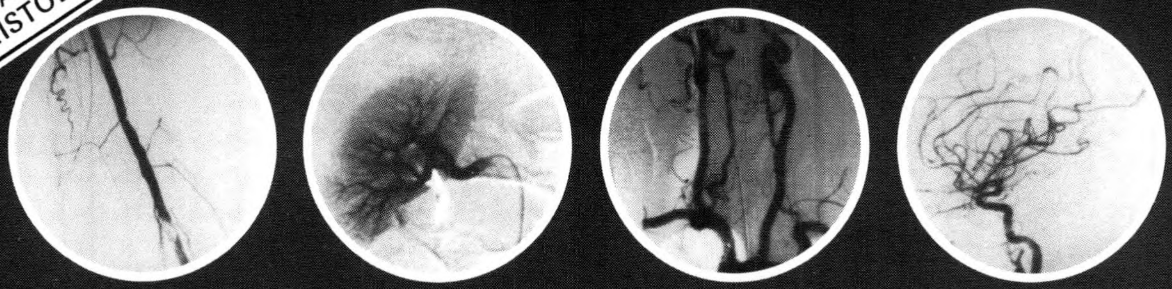

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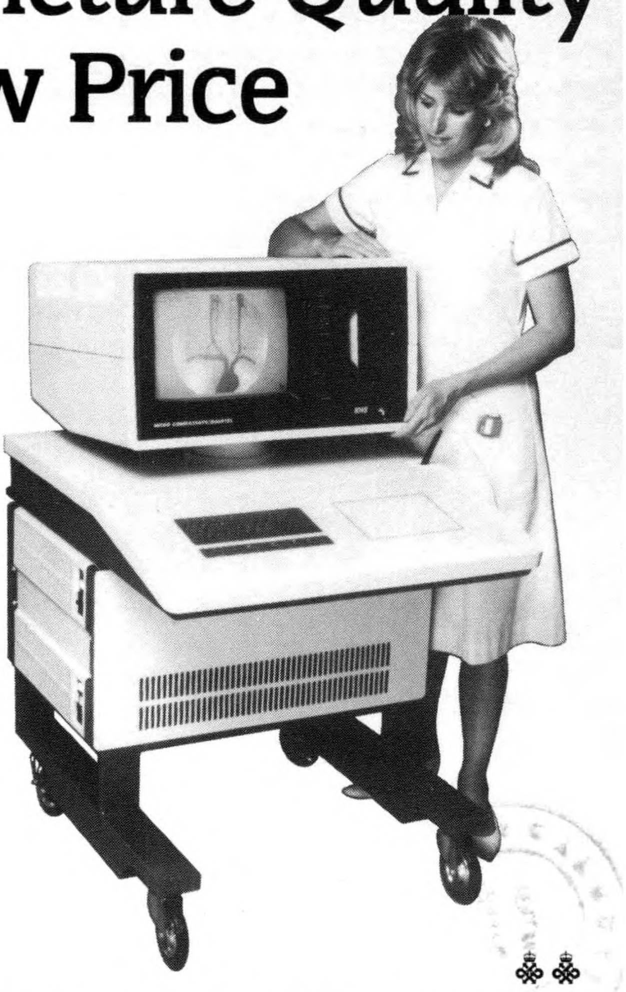

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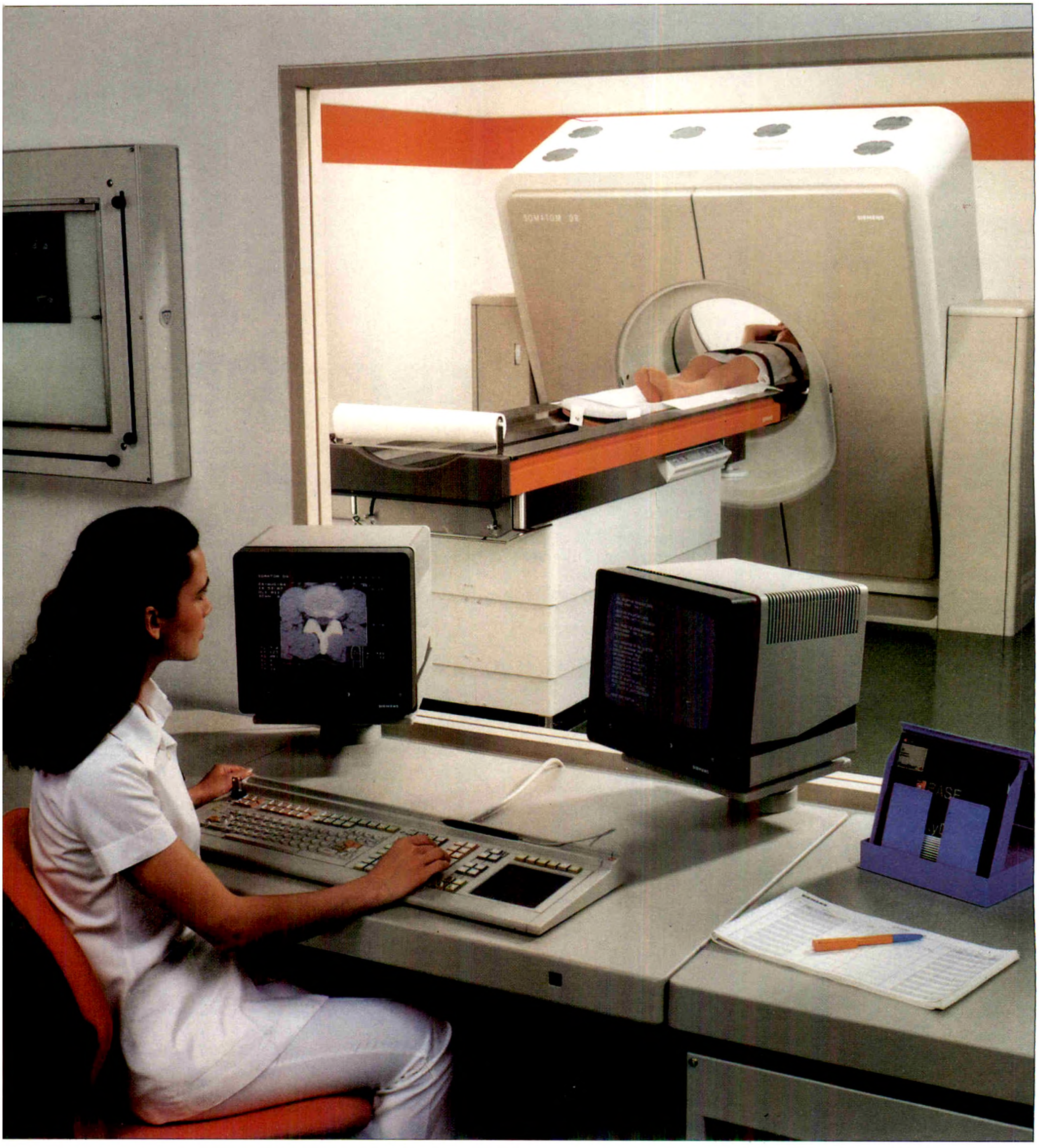

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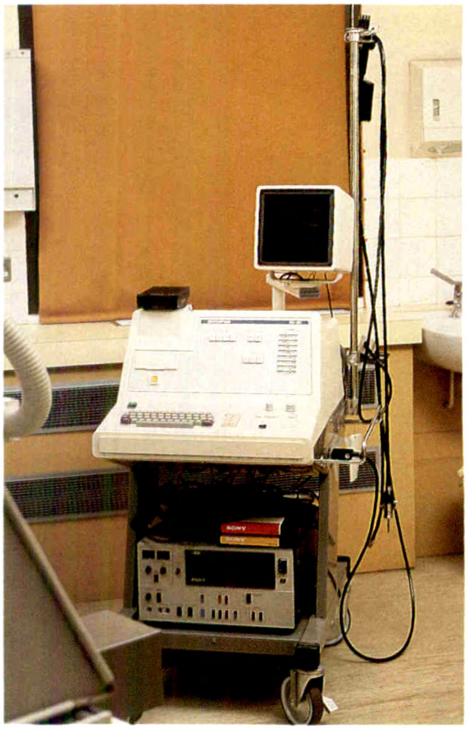

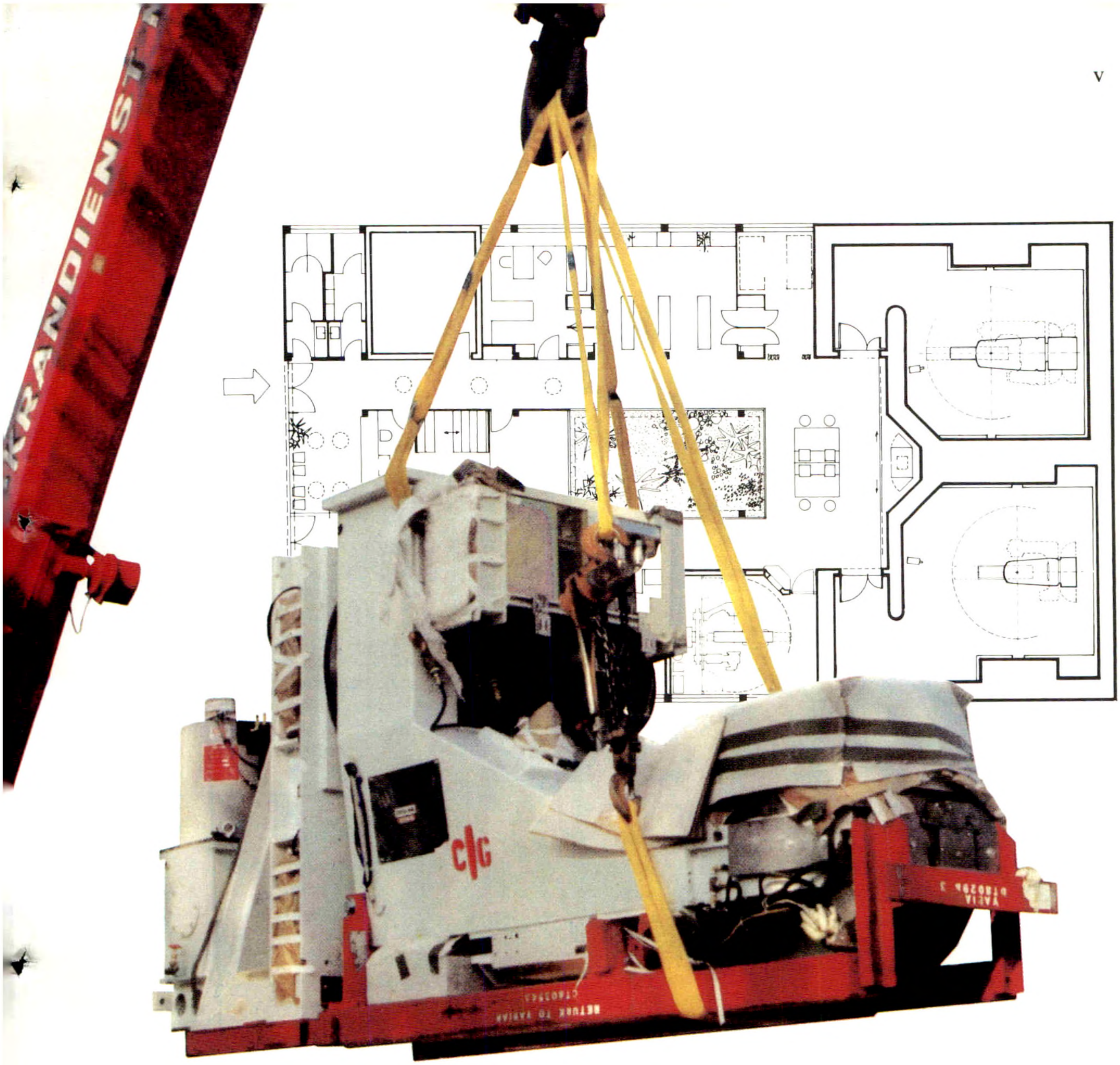

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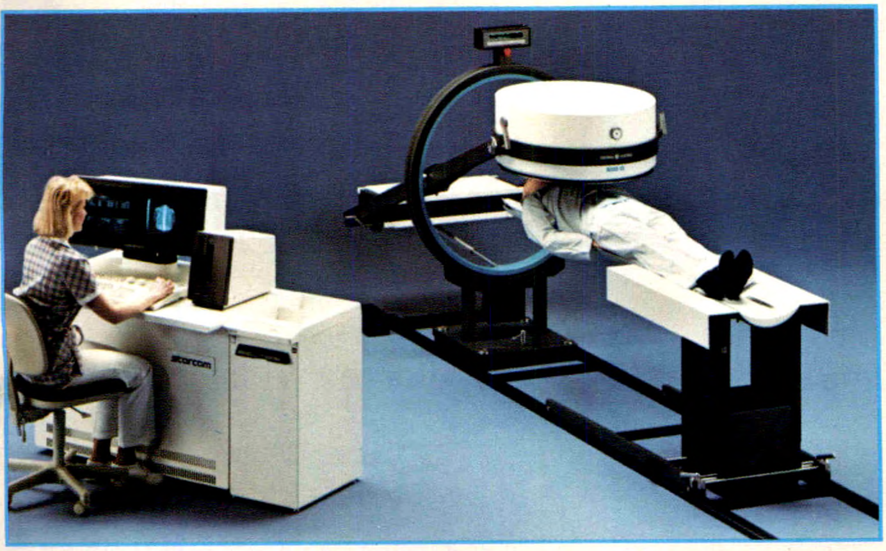

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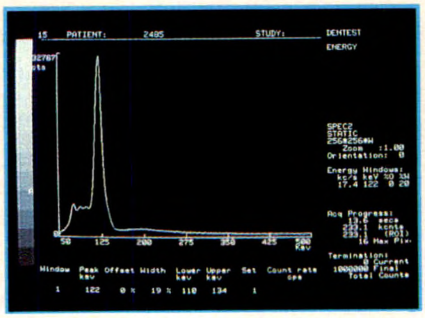


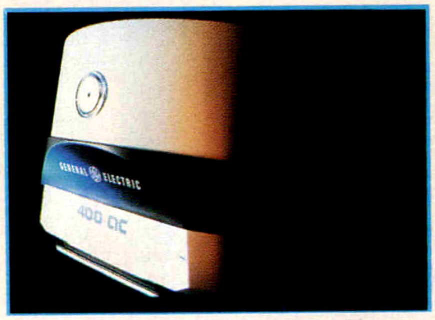
```
15   PATIENT:       2485                  STUDY:          DENTEST
                                                          ENERGY
32767
                                                          SPEC2
                                                          STATIC
                                                          256*256*W
                                                            Zoom     :1.00
                                                          Orientation:  0

                                                          Energy Windows:
                                                            kc/s keV %O %W
                                                            17.4 122  0 20

                                                          Acq Progress:
                                                               13.6  secs
                                                              233.1  kcnts
                                                              233.1  (ROI)
                                                                 16 Max Pix.
     50    125    200    275    350    425    500
                                                Kev       Termination:
                                                                0 Current
Window  Peak  Offset  Width  Lower  Upper  Set  Count rate  1000000 Final
        kev                  kev    kev           cps         Total Counts

   1     122    0 %   19 %   110    134     1
```

Starcam allows precise digital control of all detector parameters for up to three energy windows.



Starcam is available in 300, 400 (shown) and 500 mm configurations.

GENERAL ELECTRIC
U.S.A.

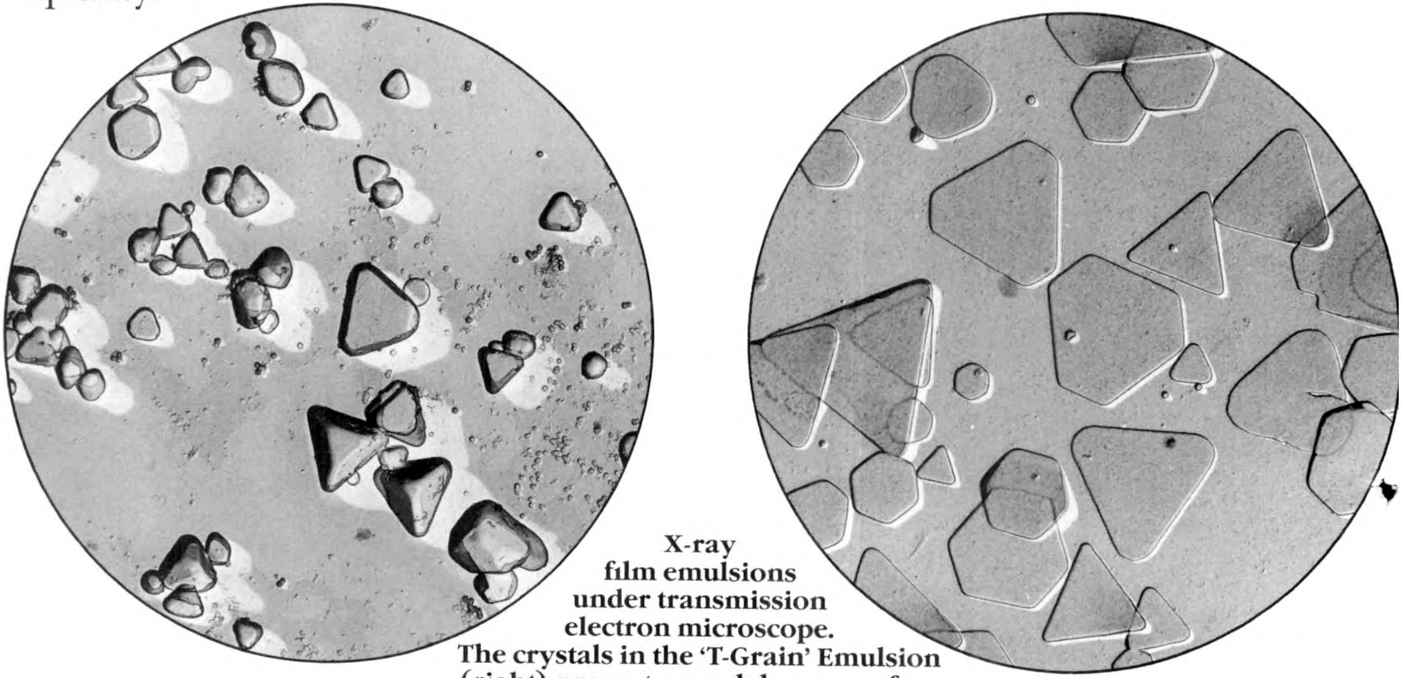
---

not connected with the English Company of a similar name.

KODAK 'T a dramatic breakthroug means sharpe

Kodak believes that conventional radiography should keep pace with other diagnostic technologies.

That belief has paid off with a remarkable advance in X-ray image quality.



X-ray film emulsions under transmission electron microscope. The crystals in the 'T-Grain' Emulsion (right) present a much larger surface area to the image source.

The 'T-Grain' Emulsion

Until today, the silver halide grains in X-ray film have always been pebble-shaped.

Kodak scientists have discovered how to grow the crystals in a flat tablet shape and to position them in the emulsion so the flat surfaces face towards the image source.

Each crystal absorbs more photons, in the same way that an open umbrella catches more drops of rain than a closed one. The result is a much greater light-gathering ability, but without increased graininess.

Reduced cross-over exposure

Because of the wider surface they present to the light, the new tablet-shaped grains absorb more of the incident light than conventional grains.

Green sensitizing dye increases this absorption.

And the higher the degree of cross-over absorption, the better the sharpness.

More diagnostic information

There's an improvement in sharpness and definition you'll be able to see at once: significantly better resolution

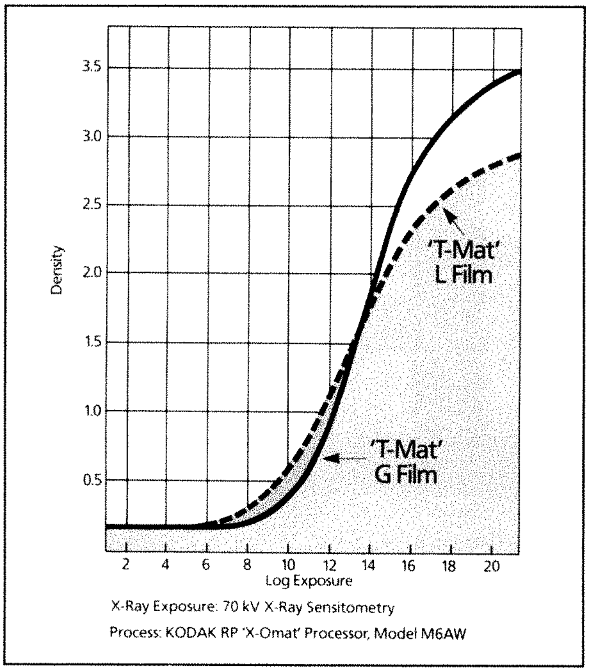
Mat' Films:
in emulsion technology
r radiographs.

and lower mottle, which means more information is available to assist accurate diagnosis.

Achieved without losing speed or changing technics.

A new family of X-ray films

Kodak is putting this latest development in emulsion technology into a complete range of films.



Characteristic curves of the two general-purpose 'T-Mat' X-ray Films give you contrast variations for different diagnostic purposes.

At present there are just two available: both can be considered as general-purpose films, but there is a significant difference in latitude.

KODAK 'T-Mat' G Film is a high-contrast general-purpose film, ideal for bone detail in orthopaedic work.

KODAK 'T-Mat' L Film is a wide-latitude general-purpose film, with an extended tonal range, ideal for soft-tissue visualization.

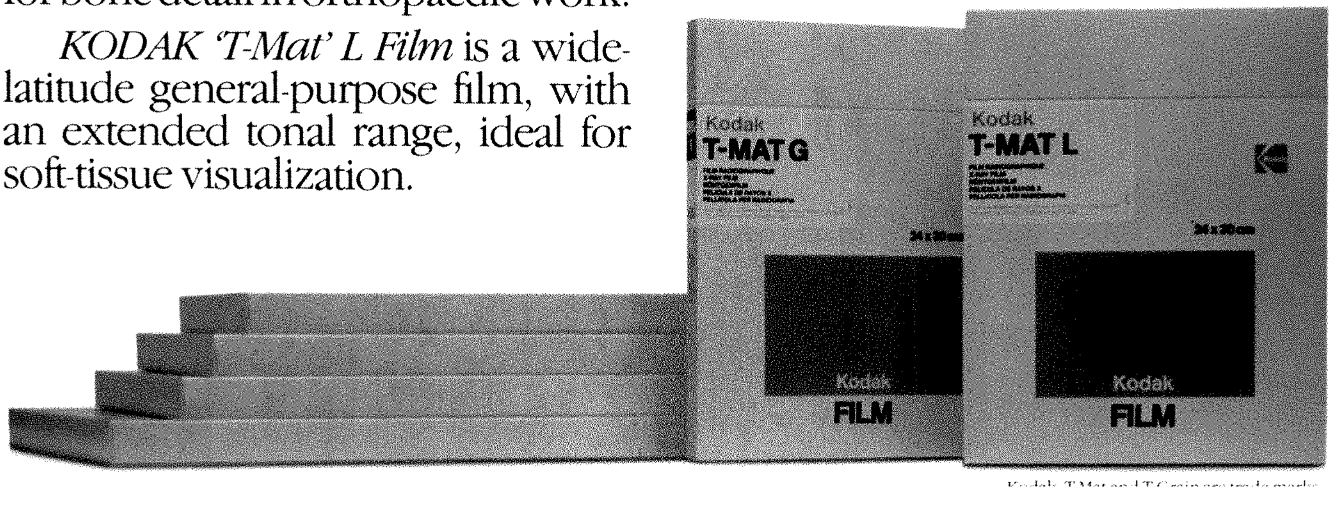
Easy to use

KODAK 'T-Mat' Films are fully compatible with KODAK (green-emitting) Intensifying Screens and other manufacturers' equivalents. And they're far less sensitive than most films to developer temperature and condition.

That makes the films easy to demonstrate on your premises, using your chemistry and screens.

Talk to your Kodak representative. And expect to be impressed.

Kodak. We care about your image.



Kodak, 'T-Mat' and 'T-Grain' are trade marks

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In the hushed corridors of hospitals and clinics, those who have bought protective lead products from BLM Girdler are loud in our praises.

That's mainly because of our comprehensive range across three areas of application.

Storage – safes, trolleys, pots
Shielding – mobile and static shields, benches, screens
Structures – bricks, cubicles, doors, panels, linings.

From isotope carriers and bed shields to complete lead-lined rooms for X-ray protection, we design and manufacture everything to the highest standard.

The other reason is our service to hospital administrators and specifiers, based on close co-operation and considerable expertise.

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BLM **BLM Girdler** **Billiton**

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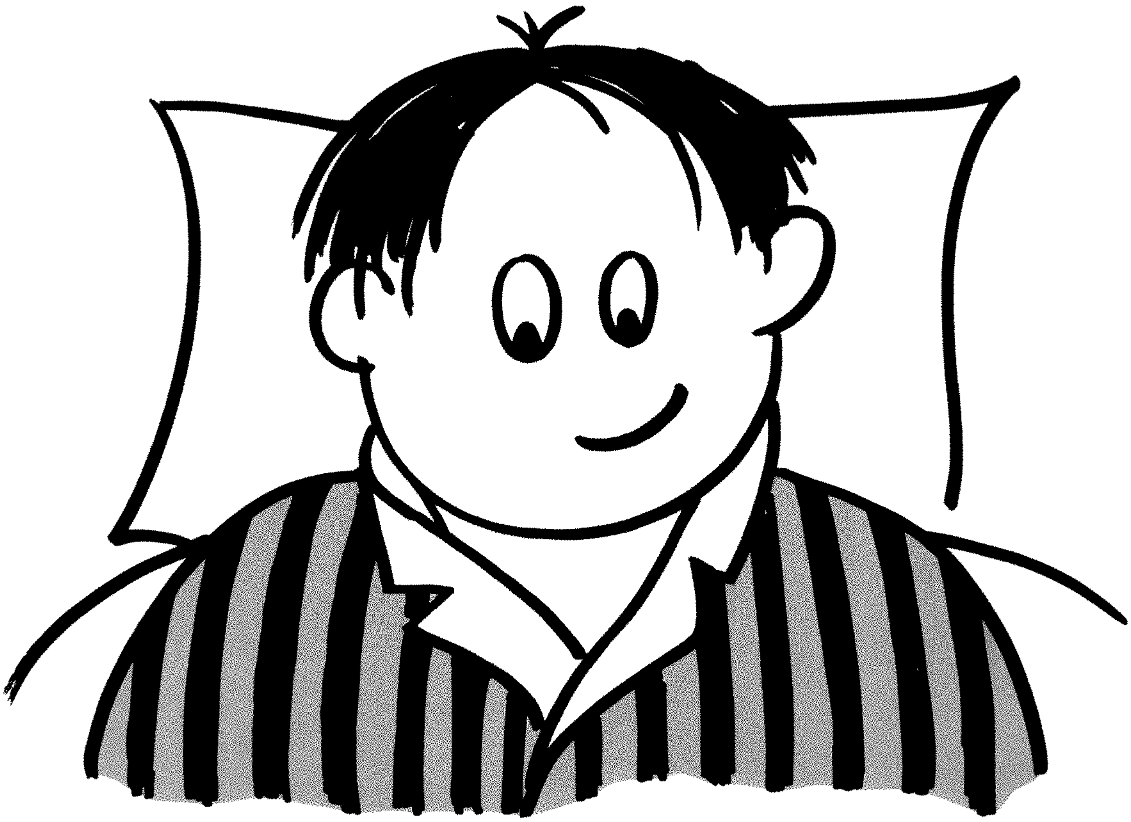
EASY EXAMINATIONS WITH NUBAIN* ANALGESIA



☐ strong, effective non-MDA analgesic, suitable for use during endoscopy or colonscopy and radiological and gynaecological investigations
☐ "ceiling" effect to respiratory depression reduces risks associated with opioid use[1]
☐ minimal effect on cardiac haemodynamics when used during catheterization[2]
☐ allows more accurate diagnosis of bile duct and gut obstructions due to minimal interference with function[3] and motility[4]

NUBAIN*
nalbuphine hydrochloride
Effective, comfortable analgesia during clinical investigations

Prescribing Information
Presentation: Nubain* Injection. 20mg of nalbuphine hydrochloride in 2ml ampoules.
Uses: For the relief of moderate to severe pain.
Dosage and Administration: 10-20mg for a 70kg individual, adjusted according to the severity of pain, physical status of the patient and concomitant medications. Nubain is not recommended for children.
Contra-indications: Hypersensitivity to Nubain.
Precautions and Warnings: Use with care in known and potential opioid abusers. Also care in active patients who may drive or operate machinery. Caution in patients with impaired respiration. Safety for use in myocardial infarction is not yet established. Caution and dose reduction in patients with impaired renal or hepatic function. Safe use not established in pregnancy and in conditions of raised intracranial pressure. Abrupt discontinuation of chronic therapy may produce withdrawal symptoms.
Side Effects: The most frequent reaction is sedation. Also sweating, nausea, vomiting, dizziness, dry mouth, vertigo and headache and other opioid effects may occur.
Product Licence No.: 4524/0003. **NHS Price:** £11.60 per box of 10 x 2ml ampoules.

References: 1. Julien RM. Effects of nalbuphine on normal and oxymorphone – depressed ventilatory responses to carbon dioxide challenge. Anaesthesiology 1982; 57: No 3A. 2. Fahmy NR, Sunder N, Soter NA. A comparison of histamine releasing properties and hemodynamic effects of morphine and nalbuphine in humans. Anesth Analg 1984;63:175. 3. Vatashsky E, Haskel Y. The effect of nalbuphine (Nubain®) compared to morphine and fentanyl on common bile duct pressure. Curr Ther Res 1985;37,1:95-102. 4. Shah M, Rosen M, Vickers MD. Effect of premedication and diazepam, morphine or nalbuphine on gastrointestinal motility after surgery. Br J. Anaesth. 1984;56: 1235-8.
Further information is available on request from Du Pont (UK) Limited, Pharmaceuticals, Wedgwood Way, Stevenage, Hertfordshire SG1 4QN. Telephone: (0438) 734549.
Nubain* is a registered trade mark of E.I. du Pont de Nemours and Co. Inc.

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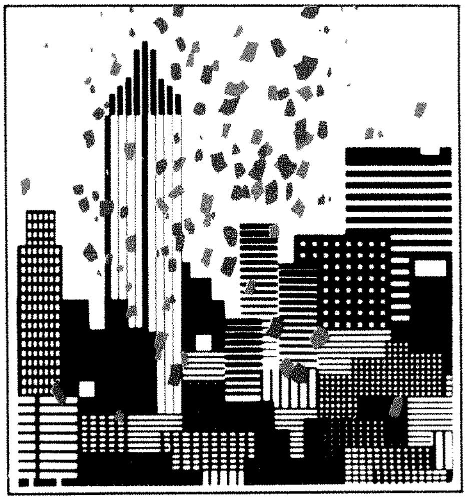
in
Low Osmolality



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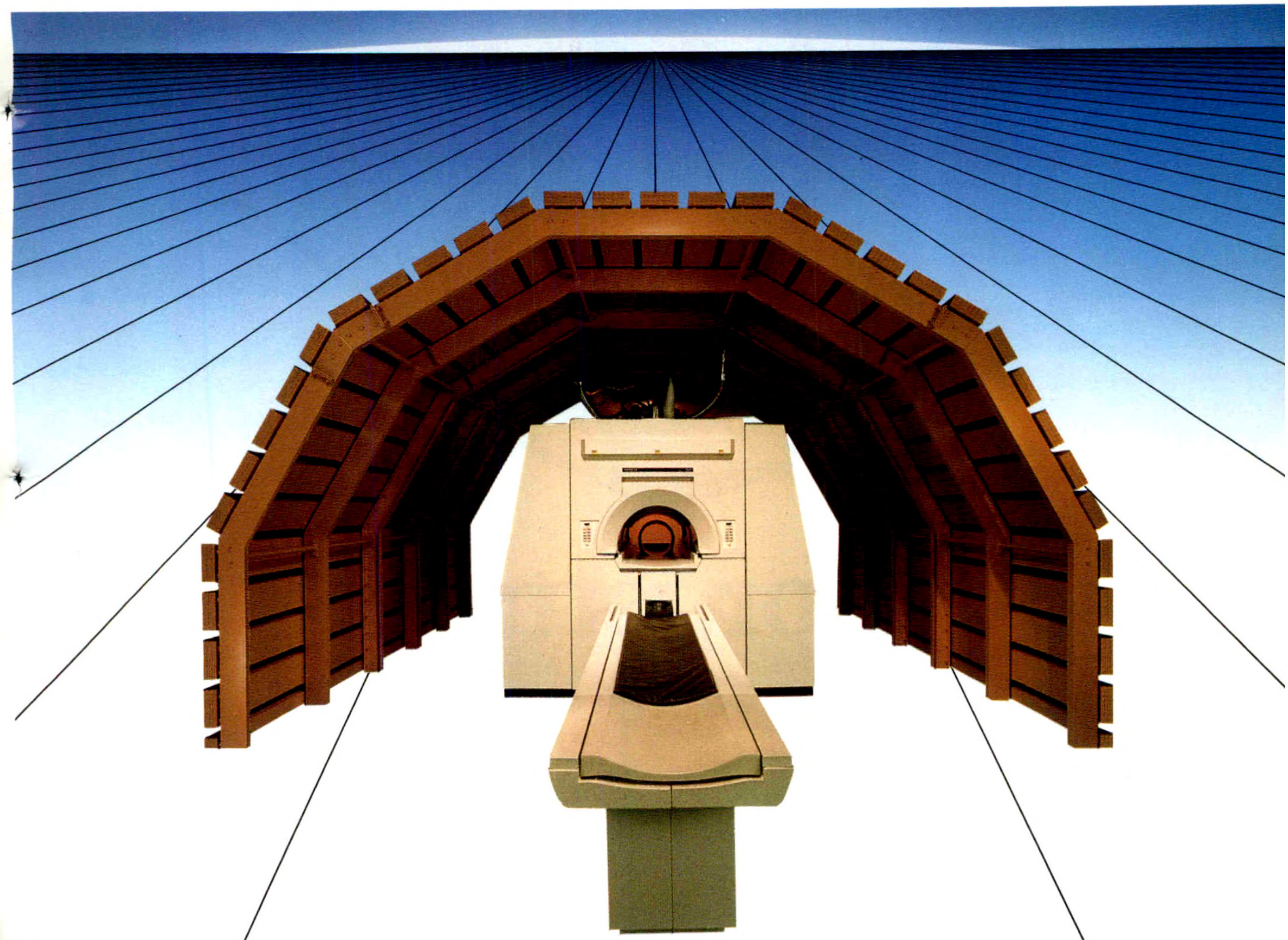
Prescribing Information Dosage: According to procedure (See Data Sheet). **Contra-indications:** Must never be injected by subarachnoid or epidural route: myelography. **Precautions:** Patients known to suffer from allergy, asthma, severe cardiovascular disease, advanced renal disease, diabetes and myelomatosis. Pregnancy. **Side-effects:** Mild warmth, metallic taste, nausea, vomiting, headache, hypotension and urticaria have been reported occasionally. **Presentations:** Meglumine ioxaglate 39.3% w/v and sodium ioxaglate 19.65% w/v injection solution (320 combined iodine per ml) in boxes of 10 × 20ml ampoules, 10 × 50ml bottles and 10 × 100ml bottles. **Package Quantities and Hospital Prices:** Boxes of 10 × 20 ampoules £35.15. Boxes of 10 × 50ml bottles £87.87. Boxes 10 × 100ml bottles £167.00 (March 86). PL No. 0012/0135. *Hexabrix 320 is a registered trade mark.



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leadership in image and quality.

When the stakes are high, it's best to bet on certainties… And with GYROSCAN, one thing you can be certain of is Philips' commitment to the future of magnetic resonance as a routine diagnostic modality.

A commitment to all aspects of MR systems operation from initial site planning and consultancy, through staff training, on-site application assistance, world-wide service organization and immense R & D effort, including cooperative agreements with many of the world's leading medical institutes, to ensure that your MR system is a responsible investment from the first day.

GYROSCAN systems from Philips are optimized for clinical diagnosis as a normal routine: excellent image quality, user- and patient-friendliness, and high patient throughput result in increased diagnostic efficiency as well as cost-effectiveness. And there's the option of a high field strength system with the capability for clinical research as well as routine diagnosis.

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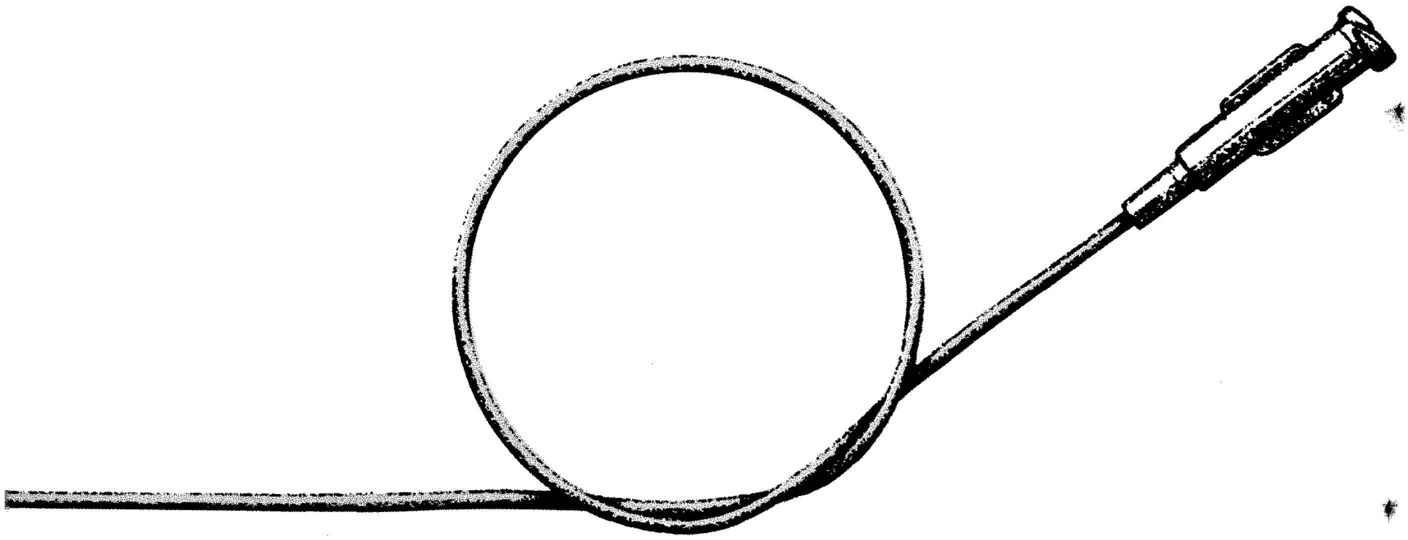

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The new range of catheters from E. Merck offers you an outstanding combination of properties.

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Flexibility, manoeuvrability, and high flow rates – an outstanding combination.

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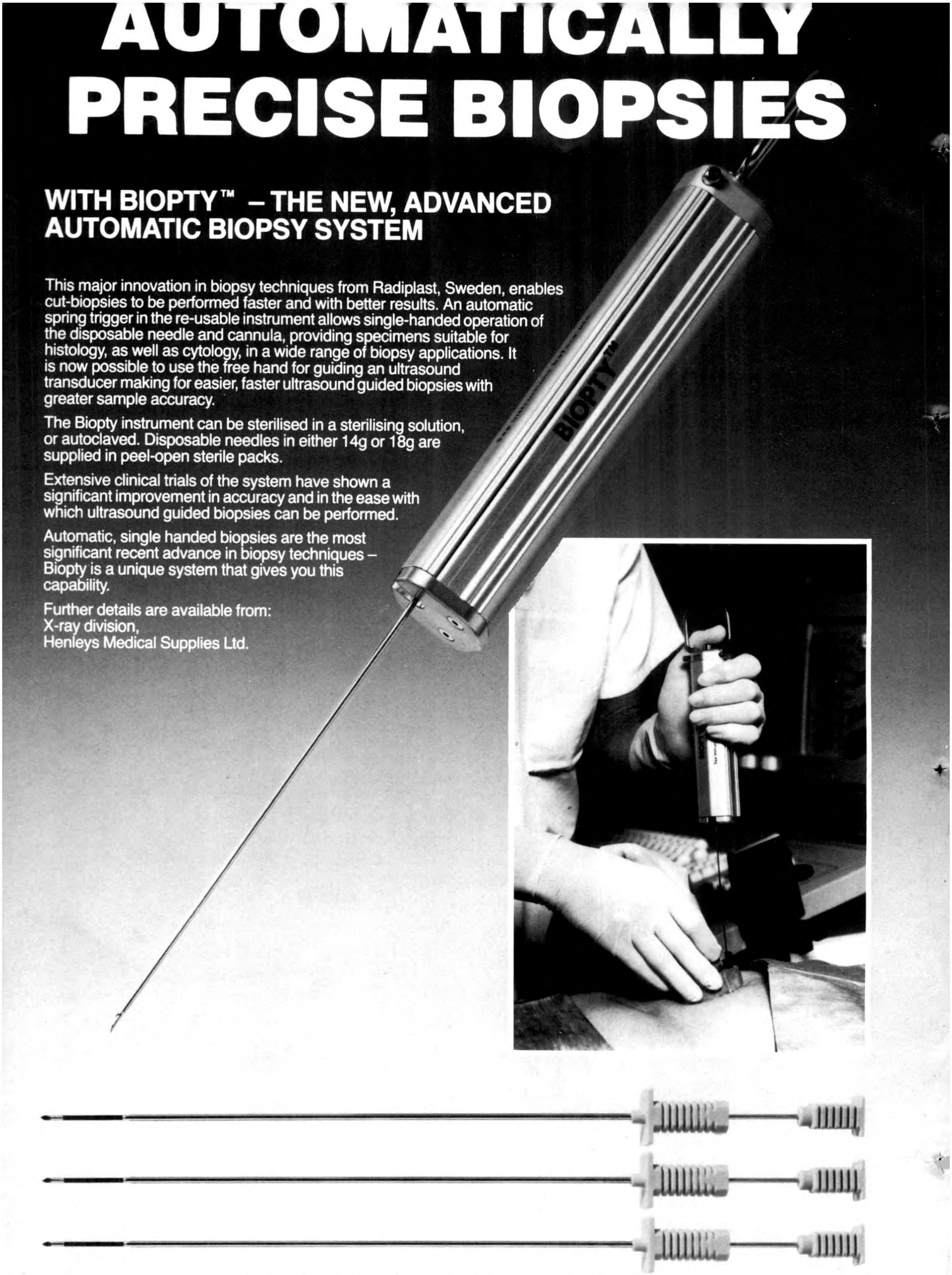

AUTOMATICALLY PRECISE BIOPSIES

WITH BIOPTY™ – THE NEW, ADVANCED AUTOMATIC BIOPSY SYSTEM

This major innovation in biopsy techniques from Radiplast, Sweden, enables cut-biopsies to be performed faster and with better results. An automatic spring trigger in the re-usable instrument allows single-handed operation of the disposable needle and cannula, providing specimens suitable for histology, as well as cytology, in a wide range of biopsy applications. It is now possible to use the free hand for guiding an ultrasound transducer making for easier, faster ultrasound guided biopsies with greater sample accuracy.

The Biopty instrument can be sterilised in a sterilising solution, or autoclaved. Disposable needles in either 14g or 18g are supplied in peel-open sterile packs.

Extensive clinical trials of the system have shown a significant improvement in accuracy and in the ease with which ultrasound guided biopsies can be performed.

Automatic, single handed biopsies are the most significant recent advance in biopsy techniques – Biopty is a unique system that gives you this capability.

Further details are available from:
X-ray division,
Henleys Medical Supplies Ltd.

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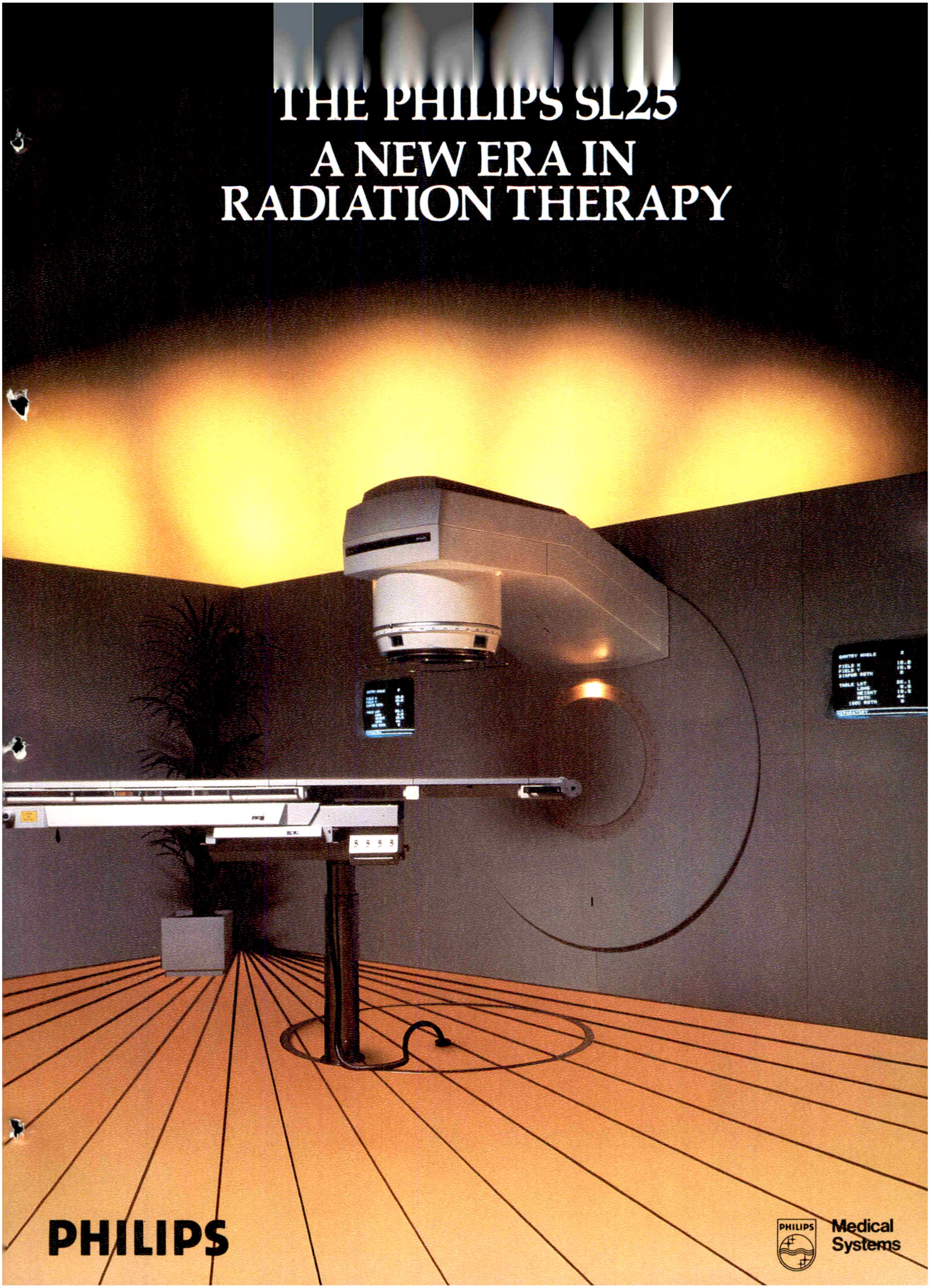
A NEW ERA IN RADIATION THERAPY



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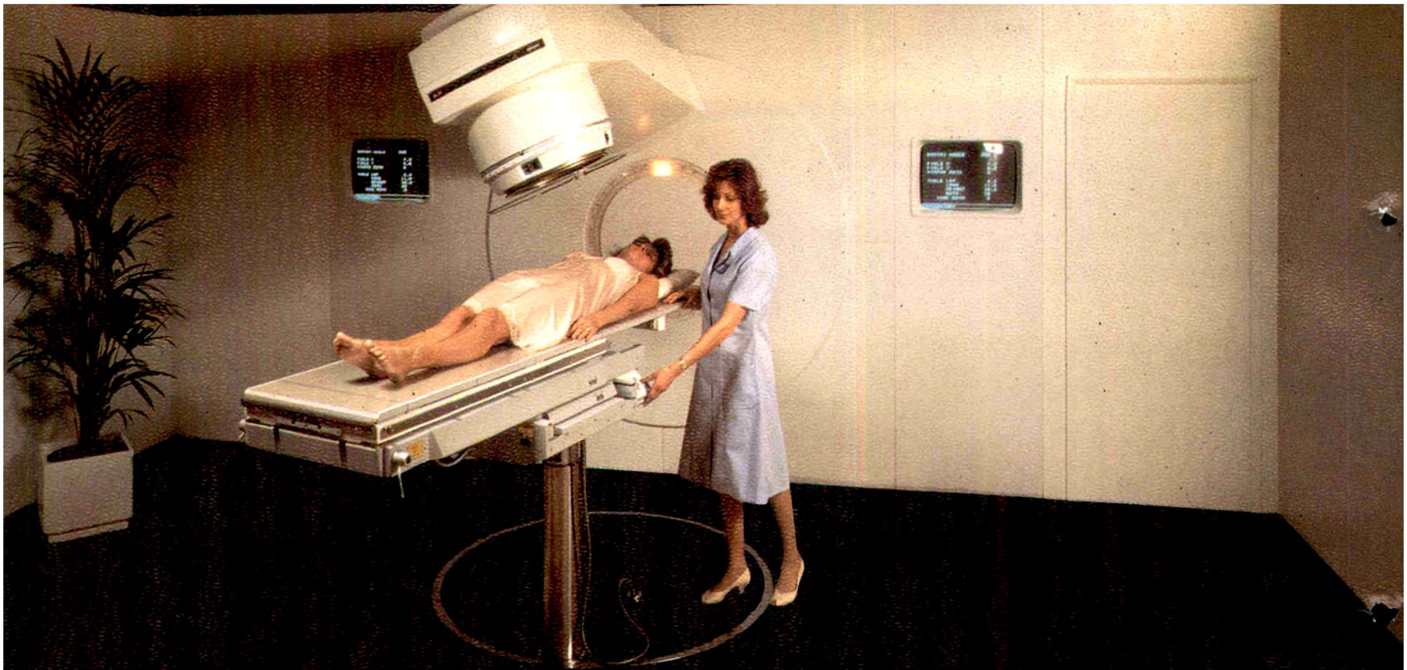
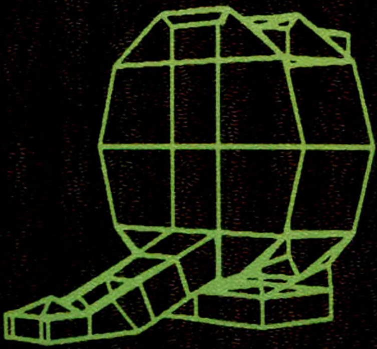
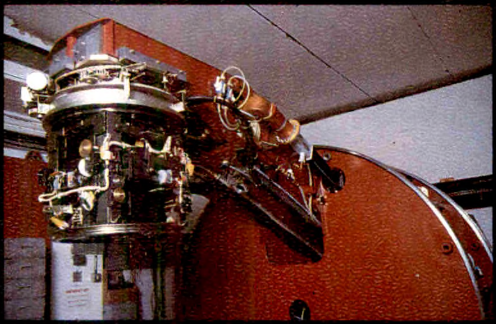


New compact Drum Gantry

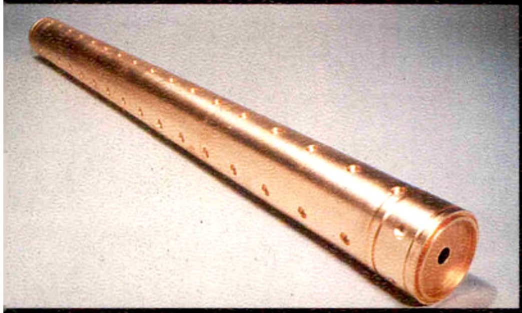
- Computer designed, providing long-term isocentric accuracy and structural rigidity.
- Rapid access for routine maintenance.

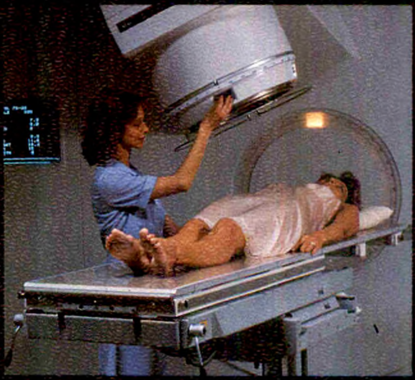




Travelling waveguide of computer-optimised design

- No need for waveguide replacement.

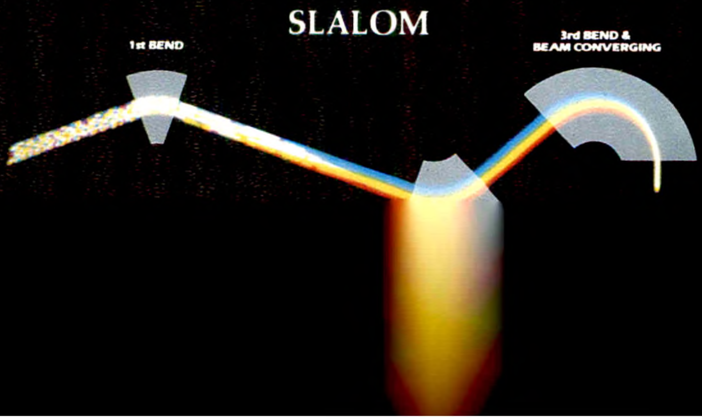




Rapid convenient setting-up with fibre optics laser back pointer available.

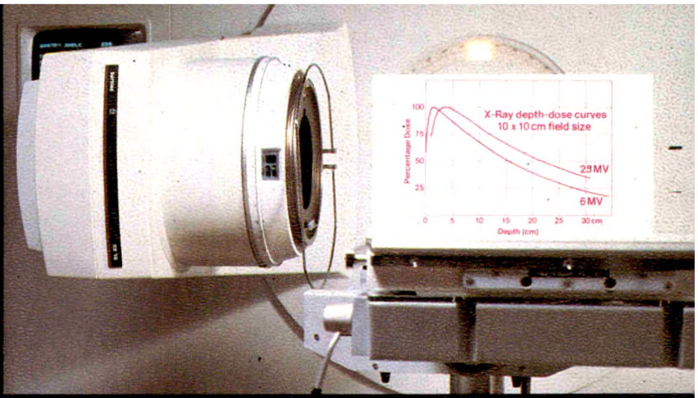
SLALOM: An entirely new approach to beam bending

- Accurate energy selection, giving stable depth-dose characteristics and excellent beam uniformity at all depths.
- Precise beam definition with minimal penumbra.
- Compact size, resulting in a conveniently low isocentre height of only 125 cm

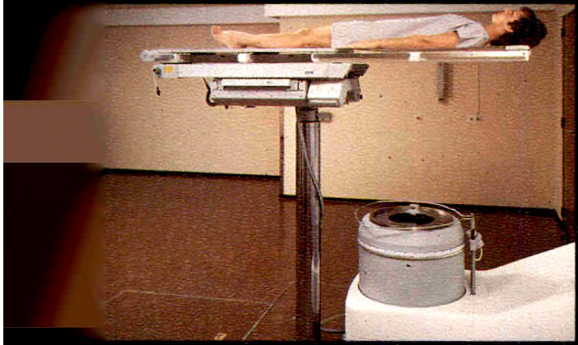


Dual X-Ray Energy Facility: 6 and 25 MV

- Exceptional range of X-Ray Dose Distributions.
- The SL25 covers the full range of X-ray treatment requirements for deep-seated, intermediate and shallow lesions.
- High Dose rates at both energies.
- Energy- and modality changeover performed within seconds.



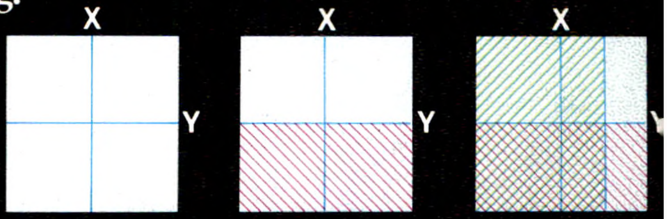
Outstanding versatility for large X-Ray field treatments



- 40 x 40 cm maximum field size in isocentric plane.
- Excellent extended-distance treatment capability.

X-Ray diaphragms with field-offset capabilities: Outstanding flexibility in beam-positioning.

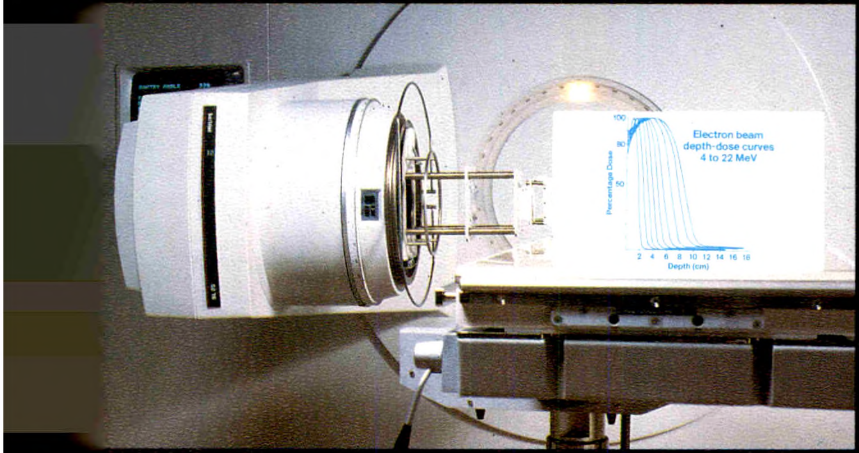
- Simplifies the abutment of adjacent fields with negligible field overlap.
- Facilitates delivery of boost doses to peripheral regions without moving the patient or gantry.
- Reduces beam divergence for shallow tangential arcs, minimising dosage to sensitive underlying tissues.
- Reduces the need for inconvenient external beam blocks.

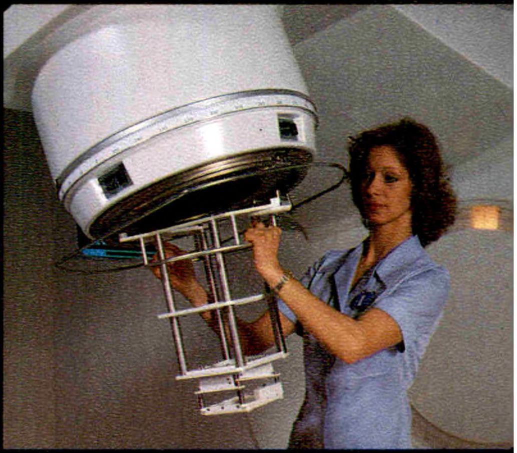


X- and Y-Diaphragms in Symmetric Mode

X-Diaphragms in Offset Mode Y-Diaphragms in Symmetric Mode

X- and Y-Diaphragms in Offset Mode





Nine Electron energies from 4 to 22 MeV: An unprecedented selection.

- Outstanding range of electron beam penetration for all treatment requirements.
- Superbly sharp dose fall-off and excellent field uniformity resulting from the Twin-Turret Dual-Scatter System combined with the totally new open-side applicator design.
- Dose calibration factor stability ensured by the sealed ionisation chamber.
- Comprehensive range of square, rectangular and circular applicators from 2 cm diameter to 25 x 25 cm square.
- Optional provision for intra-operative electron

THE MOST VERSATILE CONTROL SYSTEM

Standard provision of:

- Preparation/Update of treatment prescription.
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- Automatic self-logging of machine data.
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- Remote-Controlled Dual-Exposure Check-Radiographs.
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Plus provision for future connection to a hospital computer.

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PHILIPS Sure sign in radiation therapy PHILIPS Medical Systems

THE DOSE MANAGEMENT SYSTEM THAT PHYSICISTS CAN'T MANAGE WITHOUT.

The Ionex Dosemaster is what every Physicist has been looking for.

It is a more sophisticated and less laborious way to calibrate, monitor and record radiation dose.

As an all new and all embracing dose management system, the Dosemaster goes way beyond the capabilities of any ordinary dosemeter.

MORE FACTS AND FIGURES

Dosemaster comprises a visual display, dedicated function keys and a numeric keypad.

And for the physicist, it will fill its 9in. CRT screen with integrated dose, mean dose rate, elapsed time, all correction factors applied and calibration data. All this in large, clear numerals and with a choice of units – "R", "rad", "rem", "C/kg", "Gy" or "Sv".

Without prompting, the Dosemaster will highlight any out-of-limit parameters and will even double check its own readouts. And then, on request, it will print a complete report of the measurement with all relevant information included.

Dosemaster stores all ionisation chamber parameters in its memory and on entering the chamber serial number these parameters are brought into use. However, without knowledge of the password no changes or additions to the stored information are possible.

In short, it provides the means to calibrate and measure radiation, at all levels both accurately and quickly.

DUAL-CHANNEL MODEL

The two-channel model is ideal for ratio techniques and may also be used for two simultaneous and completely independent measurements.

So, if you are a medical physicist then get onto a good thing: get on the 'phone and ask us about the Dosemaster – NOW!

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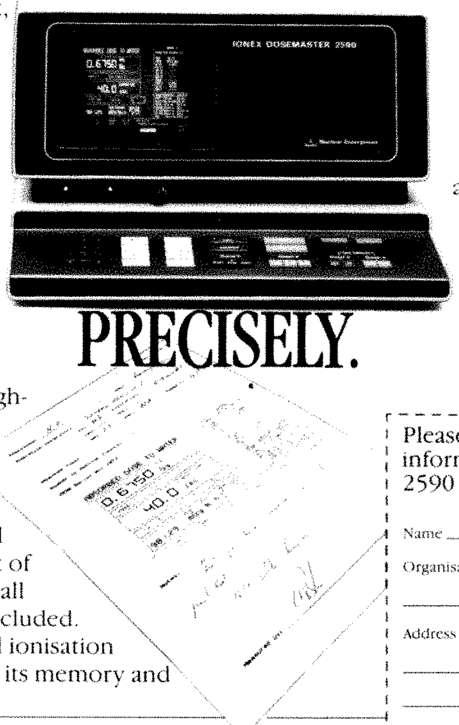

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Criteria and Methods for Quality Assurance in Medical X-ray Diagnosis

Proceedings of a Scientific Seminar organised by the Commission of the European Communities and the Centro di Ricerca Applicata e Documentazione, held in Udine, Italy, 17–19 April 1984

British Journal of Radiology Supplement 18

The contributors to this Seminar came from 15 European countries, the USA and Canada. All aspects of Quality Assurance were discussed: the concepts and implementation of QA, the involvement of research, professionals, industry and governments, and the technical aspects of equipment testing, image quality, information content and dose- and cost-reduction.

The proceedings give an up-to-date picture of the state of the art in QA and will be of interest to radiologists, radiographers, health physicists, radiation protection scientists, equipment manufacturers and administrators of health care programmes and radiation protection.

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Expanding horizons of diagnostic ultrasound

9–21 November 1986 in London

This course is designed to explore recent developments in the clinical applications of diagnostic ultrasound. The potential and limitations of the technique will be illustrated and the relationship of ultrasound to other diagnostic imaging methods will be discussed.

Two and a half days will be allocated for visits to Diagnostic Ultrasound Departments at the Middlesex and Royal Marsden Hospitals and to the Obstetrics Department at King's College Hospital.

The course will be jointly directed by **Dr H B Meire**, Consultant Radiologist at King's College Hospital, London and **Dr P N T Wells**, Chief Physicist at Bristol General Hospital.

Applicants should be of consultant or senior registrar status or should be senior paramedical personnel. Applicants should preferably have one or two years' experience of applied clinical ultrasound. The more experienced participants may be invited to make short presentations during the course on appropriate topics.

There are vacancies for 30 participants.

Fee £895 Residential, £585 Non-residential.

The course lectures and discussions will take place at a hotel in Central London. Residential course members will be accommodated at the same hotel.

Further information and application forms are available from British Council Representatives overseas or from Courses Department, The British Council, 65 Davies Street, London W1Y 2AA

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Patient Dose Monitor and Beam Analyzer

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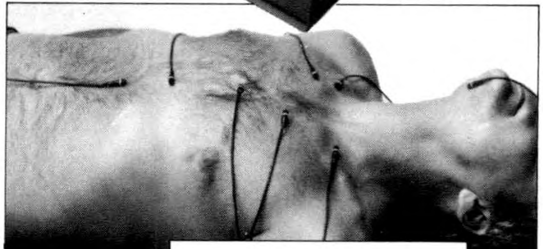
Dosimetry System



```
        PATIENT DOSE MODE
DATE __11/25/85_______________
TREATMENT _AP MANTLE__________
USING DETECTOR SET A
PATIENT
______MARY DOE________________
BY __JACK SMITH_______________

DETECTOR      LOCATION       DOSE
--------      --------       ----
1(ALM)RED   CHIN_____________  15
2 ORANGE    LT NECK_________  215
3 YELLOW    RT NECK_________  216
4 LT GRN    LT SUPRACLAV____  208
5 DK GRN    RT SUPRACLAV____  213
6 LT BLUE   LT AXILLA_______  215
7 DK BLUE   RT AXILLA_______  215
8 BLK       CENT AXIS_______  203

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350 UNIT/MIN

CORRECTION FACTOR IS 1.000
ALARM SETTING IS 20
ALARM IS ENABLED
```

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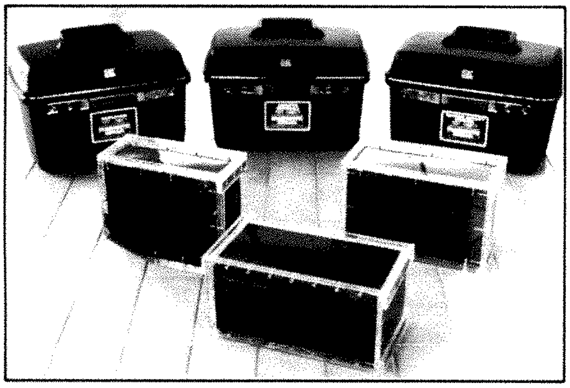

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Radiation Damage to Skin

Fundamentals and Practical Aspects

Proceedings of a Workshop held at Saclay, France, on October 9–11, 1985, organised by the Commission of the European Communities and the Commissariat à l'Energie Atomique de Protection et de Sûreté Nucléaire, Fontenay-aux-Roses, France.

Skin and underlying tissues are frequently critical structures in radiological protection. Over exposure to ionising radiation can cause serious long-term suffering and disability.

Despite their practical importance, the dose-effect relationships, the pathophysiological mechanisms and the influence of the degree to which different tissues are involved are still poorly understood.

This Workshop and Proceedings bring together those at the forefront of research in these areas from all over the world. They review the present state of knowledge and attempt to identify specific problem areas which may lead to recommendations for the improvement of radiological protection and for the better management of radiation accidents.

Radiation Damage to Skin is, therefore, a vital reference work for everyone working in radiation protection and dosimetry.

Price £18.00 including postage and packing. About 200 pp.; illustrated.

ISBN 0-905749-13-8
ISSN 0007-1285
Available June 1986

Orders to: The Publications Department, The British Institute of Radiology, 36 Portland Place, London W1N 3DG. Tel: 01-580 4085.

RADIATION ONCOLOGIST

Two posts for Staff Radiation Oncologists (one new, one due to retirement) are available at The London Regional Cancer Centre, London, Ontario, Canada. This is a multidisciplinary cancer centre which is involved in supplying clinical services to a large area of Southwestern Ontario (catchment population is 1.6 million) and sees some 2600 patients in its clinics per annum.

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Dr Peter J. Corbett
Chief, Radiation Oncology
London Regional Cancer Centre
391 South Street
London, Ontario
N6A 4G5

Telephone: 519-679-9890.

THE BRITISH INSTITUTE OF RADIOLOGY

Mayneord Lecture 1987

The Mayneord Lecture is financed through the generosity of 3M United Kingdom PLC. It is named after Professor W. V. Mayneord CBE, FRS, Past President and Honorary Member of the British Institute of Radiology. The Award is made annually to an individual or to a group of collaborators in recognition of recent or current major contributions to the wide and expanding field of radiology.

Nominations for the fourth lectureship to be delivered at Radiology '87 are invited and should include a curriculum vitae and a clear, concise statement of the work on which the lecture is to be based, which must come within the wide field of interest of the British Institute of Radiology. The recipient will be selected by a committee comprising the President and senior Vice President of the British Institute of Radiology and a senior member of 3M United Kingdom PLC. Please send nominations to the President, The British Institute of Radiology, 36 Portland Place, London W1N 3DG before *1st May 1986.*

The third Mayneord Lecture entitled **Seeing things more clearly** will be given by Mr G. R. Higson BSc, FInstP, CEng, FIEE, Director, Scientific and Technical Services, Department of Health and Social Security. It will be given at the Unicorn Hotel, Bristol, on Wednesday 9th April 1986 at 5.00 pm during the BIR Annual Congress RADIOLOGY '86.

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for foreign students to study and train in the United States

The American Society for Therapeutic Radiology and Oncology Education and Development Fund is seeking candidates for the Anna Hamann Scholarship Program.

Eligibility Rules

1. Each candidate must have completed at least two (2) years of specialised training in radiation therapy in a program outside the United States which is recognised by the board of directors of the American Society for Therapeutic Radiology and Oncology as providing suitable training in radiation therapy.

2. Close relatives of incumbent officers or directors of The American Society for Therapeutic Radiology and Oncology Education and Development Fund or of the American Society for Therapeutic Radiology and Oncology and close relatives of any person who has served as such an officer or director during the period of five (5) years immediately preceding the consideration of candidates, shall be ineligible to receive an Anna Hamann Scholarship

Criteria for selection of Anna Hamann Scholars

1. Record of achievement in prior work in the field of radiation therapy, particularly as an indication of potential for making a significant contribution to the field.

2. Extent to which the particular professional goals of the candidate would be furthered by study and training in the United States

3. Interest of the candidate in teaching or practicing radiotherapy in his or her country of origin or in another country other than the United States following the period of study and training as an Anna Hamann Scholar

4 Financial need.

5 Availability to the candidate of similar training through programs other than the Anna Hamann Scholarship Program.

6. To the extent permissible under applicable laws, the nationality of the candidate, with a view toward implementing to the extent feasible the express wish of Dr. Anna Hamann that student exchanges be promoted between Germany and other European countries and the United States.

Post-selection requirements for candidates

Before any portion of an Anna Hamann Scholarship grant may be paid to or on behalf of a qualified candidate selected by the board of directors, he or she must meet the following additional requirements·

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2. Satisfy the general requirements applicable to foreign physicians coming to the United States for postgraduate training, including passing the examination administered by the Educational Commission for Foreign Medical Graduates

3. Obtain all required permission from appropriate immigration authorities to enter the United States and to remain in the United States for the period of time required to complete the designated course of postgraduate study and training

To suggest a candidate or to request additional information, please contact William T. Moss, MD, Chairman, Department of Radiation Therapy, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, Oregon, 97201, U.S.A.

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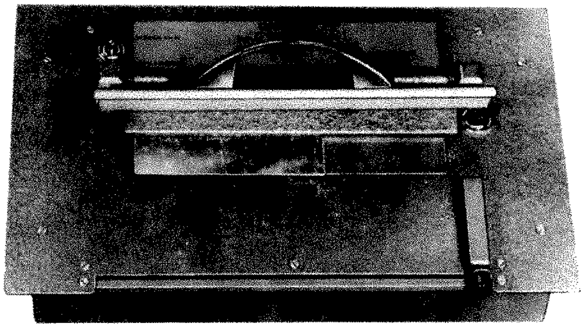

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1986, *The British Journal of Radiology*, 59, 309–315

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The British Journal of Radiology

Advances in imaging technology and their impact on medicine

The Mackenzie Davidson Memorial Lecture, April 1986*

By Alexander R. Margulis, M.D. and William J. Shea Jr, M.D.

Department of Radiology, University of California, School of Medicine, San Francisco, CA 94143, USA

(*Received October 1985*)

The last decade has witnessed an unprecedented and explosive expansion of new modalities in diagnostic imaging To a great extent this is the result of the investment of governments in weapons research and space and energy exploration. These have produced significant breakthroughs and advances in microcomputers, microcircuits, telecommunications and miniaturisation of equipment. The impact of the application of the new imaging modalities has been significant The patient flow is changing from predominantly in-patient to largely ambulatory as diagnostic examinations have become less and less invasive. Even some therapeutic procedures have shifted from the operating room, where anaesthesia was required, to the high-technology imaging suite where interventional radiologists remotely control instruments, with the help of one of the imaging modalities. These changes are accelerating as technological advances continue and the benefits are so obvious that even the most severe critics are challenging not their benefits but their affordability in view of their rapid dissemination and high price.

Furthermore, the advances in imaging technology are occurring in an atmosphere of retrenchment in expenses and a determination on the part of society in the USA and elsewhere rigidly to control the cost of medicine

The Economy of Medicine in the USA, 1980–86

In 1984 $387.4 billion were spent on all types of health care in the US (Waldo & Lazenby, 1985). This represents 10.6% of the gross national product (GNP) (Fig. 1). (GNP is the total income from goods and services for a given year) In 1965 health-care spending accounted for 6.1% of the GNP and amounted to less than $50 billion. The $1580 per person spent on health care for Americans in 1984 is higher than the average per capita income in much of the world. Spending for hospital care amounted to $157.9 billion, representing 46% of all personal health care expenditures.

Public programmes financed 53% of all hospital care. Medicare the federal health insurance programme for the elderly and disabled, underwrote 28% of all hospital expenses. Medicaid, the programme jointly administered by the Federal and State Government for the poor, paid 9%. The public sector paid 72.1% and the individual patients 27.9% of all spending on personal health. Physician services amounted to 22% of expenditures or $75.4 billion.

Even these huge expenditures represent a slowdown from the rapid increases preceding 1982. Although the spending in 1984 grew by 9.1% from that in 1983, inflation and aging of the population accounted for much of the increase in cost.

The enormous costs of health care in the US are mirrored in the huge expenditures for hospitalisation which consume over 40% of the total. The typical costs in a large Western teaching hospital are shown in Table I.

Regulation of cost expenditures

Although the prices of the new, sophisticated imaging equipment which have been an important part of the diagnostic revolution are formidable, they still account for less than 1% of the total health care expenditure in the USA (Health Industrial Manufacturing Association, personal communication). Individually taken, however, the price of each piece of equipment is large enough to attract the attention of everyone concerned with health-care costs. The introduction of computed tomography (CT) led to the establishment of federal controls over manufacturers' introduction of new equipment through the Federal Drug Administration, and to federal and state certificates of need (CON). Computed tomography, however, turned out to be the wrong target for cost cutting. Instead of increasing expenditures, it was responsible for significant reductions in the cost of health care, in addition to reducing significantly the invasiveness of diagnostic procedures. Computed tomography has eliminated exploratory surgery in most of the US, streamlined the diagnostic work-up, and shortened the hospital stay (Newton et al, 1983). It has reduced the complication rate of surgery and in very many instances, through the visual guidance of biopsy CT, provided an immediate, precise histological diagnosis with all the resulting advantages.

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*Delivered by Professor A. R. Margulis at the 44th Annual Congress of the British Institute of Radiology, Bristol, 9–11 April 1986.

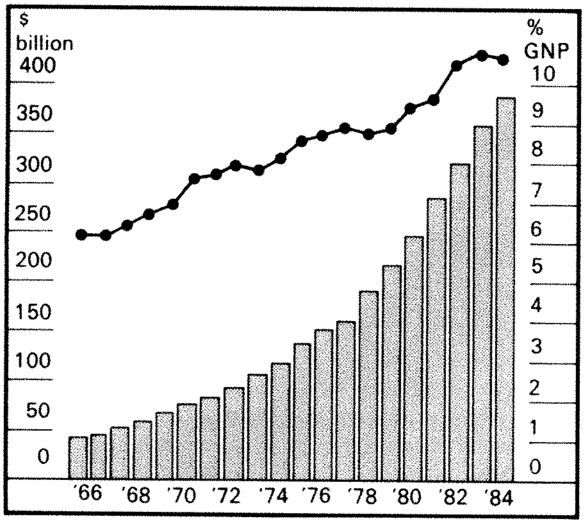


FIG. 1.

Health-care expenditures in the US for each year in $ billion and % GNP (data are from the US Department of Health and Human Services).

The consequence of these undisputed contributions of CT to the improvement of health care, in some cases even supported by court decisions, has been the gradual erosion of the CON process, with its elimination altogether in California and on the federal level. The relative success of the US Federal Government in slowing the inflation rate of health care was in part due to the introduction of diagnosis-related groups for the lump sum reimbursement to the hospital for Medicare patients. This new policy was followed by contractual arrangements made by states and private insurance companies with individual hospitals. The hospitals, physicians and other health-care providers have, thus, been forced into stiff competition.

The advances in diagnosis and treatment have, in turn, increased the efficiency of in-patient handling, shortening hospital stays and further aggravating the oversupply of hospital beds in most of the US.

The pressures from the Federal Government and organised medicine on practitioners and organisations employing physicians have resulted in keeping the practitioners' portion of the health-care expenditures stable, in spite of rising costs.

TABLE I

TYPICAL ROOM RATES IN A LARGE WESTERN TEACHING HOSPITAL, 1985 FINANCIAL YEAR

Ward	$ 413/day
Semi-private room	$ 426/day
Private room	$ 435/day
Cost per part-day	$1100*
Intensive care unit	$1409/day $2000/part-day
Operating room	$ 716/h†

*Except for surgery, where it is even higher

†Personal communication. Current rates at the University of California, San Francisco Hospitals, 1985–86.

Even the seemingly endless spiral of escalating malpractice premiums paid by physicians, because of the huge awards by courts to patients and their lawyers working on contingency, has started to be attacked by some states like California, attempting to limit the awards to a reasonable level, while at the same time regulating the portion of the award that lawyers receive from these decisions. The attempts at streamlining and reversing the trend of escalating malpractice premiums will undoubtedly be followed by other states, as the multimillion dollar awards have led to malpractice insurance premiums of $101 000 per year for neurosurgeons and over $80 000 for obstetricians on Long Island, New York (National Conference of State Legislators, 1985).

At the University of California, San Francisco, Showstack et al (1985) studied the changes in the styles of treatment with respect to the rising costs of hospitalisation between 1972 and 1982. The substitution of newer for older technologies tended to offset increases in resource use, while the substitutions of surgery for medical treatment were associated with large rises in costs. Advances in diagnostic and treatment technologies tended to supplant older, more invasive procedures. Charges for imaging services amounted to less than 10% of the total bill in all diagnoses studied. The primary factors associated with the rising costs were the substitution of surgery for medical therapy to patients admitted for acute myocardial infarction, respiratory distress of the newborn, and the provision of intensive care treatment for critically ill patients. There was no difference in survival for any diagnosis across the 10 years. Future control of hospital costs may require ethical considerations with which society must come to grips.

THE NEW MODALITIES

Ultrasound

Ultrasonography is a physician-intense, relatively inexpensive, rapid and readily available modality. Because of these characteristics, it is highly popular and is rapidly becoming an adjunct to the physical examination of many specialist practitioners. Real-time ultrasonography is an excellent screening method for diseases involving the abdomen. It is a much used method in evaluating the heart, liver, biliary tree and pregnant uterus (Fig. 2). It is also of great value in guiding biopsy needles and the introduction of drainage tubes. In addition to the screening real-time ultrasonography, high-resolution digital grey-scale sonograms are of great value in the evaluation of multiple abdominal conditions.

The most promising developments in ultrasonography, however, deal with the intrauterine diagnosis of fetal abnormalities (Fig. 3). With the rapid advances in

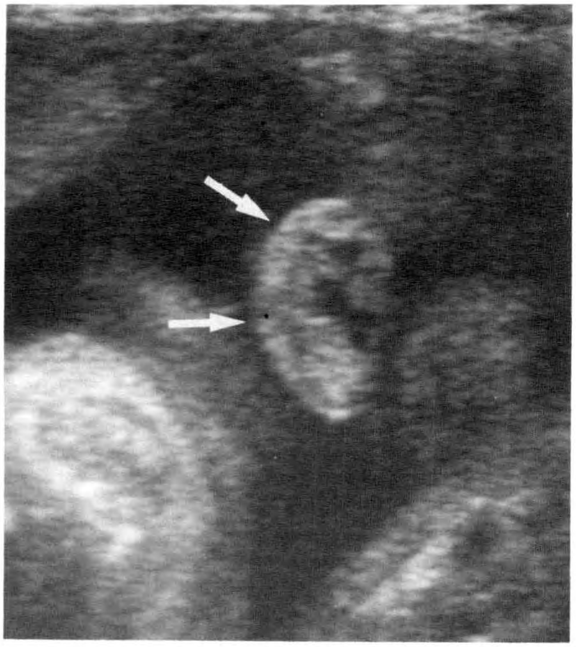


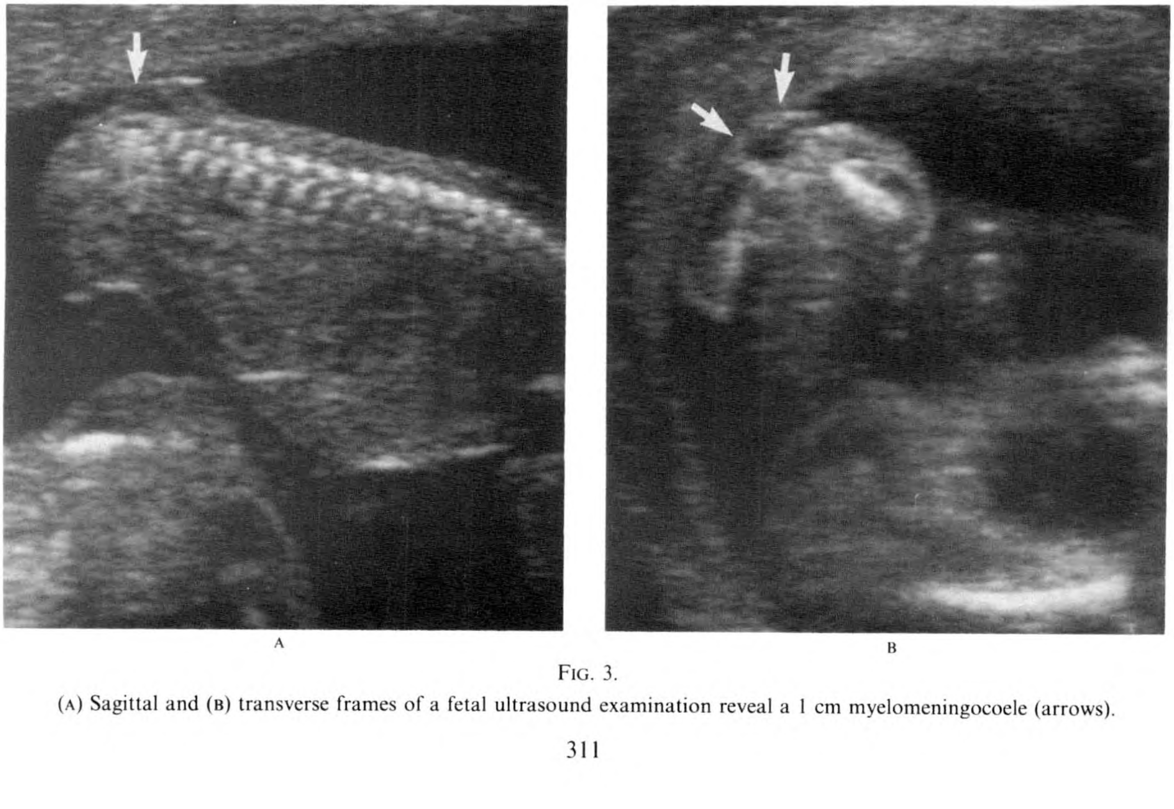
FIG. 2.
Ultrasonogram of a 3rd trimester fetus with state-of-the-art technology reveals exquisite detail of the fetal ear (arrows).

surgery on the fetus, the precision of ultrasonography in diagnosis is indispensable (Chinn & Filly, 1982). In spite of repeated and rather imaginative attempts at tissue characterisation by ultrasonography, the results have thus far been disappointing (Sommer et al, 1981).

Ultrasonography, because of its many advantages and, particularly, because of its speed, ready availability and low cost compared with other imaging modalities, is the favourite approach even in countries where CT and magnetic resonance imaging (MRI) are available.

Computed tomography

Ever since its introduction by Hounsfield (Ambrose & Hounsfield, 1973; Hounsfield, 1980), CT has revolutionised diagnostic approaches to most afflictions, displacing many time-honoured procedures. The wide expansion of tissue-density discrimination from that offered by conventional radiography, the low-noise, thin-slice tomography, the continuously improving spatial resolution and increasing speed of scanning leading finally to real-time CT, when combined with continuously falling cost of equipment make this one of the most attractive and versatile imaging modalities. Electrocardiogram gating, reformatting in any plane and improvements in detection have made CT an indispensable diagnostic tool in the industrial countries. With the diminishing cost of the procedures, the increased availability of the equipment and the rapid patient throughput, CT is increasingly encroaching on conventional radiographic procedures. The use



A

B

FIG. 3.
(A) Sagittal and (B) transverse frames of a fetal ultrasound examination reveal a 1 cm myelomeningocoele (arrows).

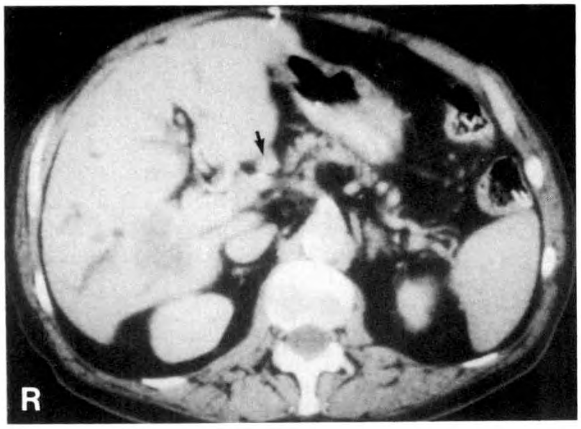


FIG. 4.

A single slice of a CT study in a patient with pancreatic carcinoma reveals liver metastasis, porta hepatis lymph node (small arrow) and (L) adrenal tumour involvement.

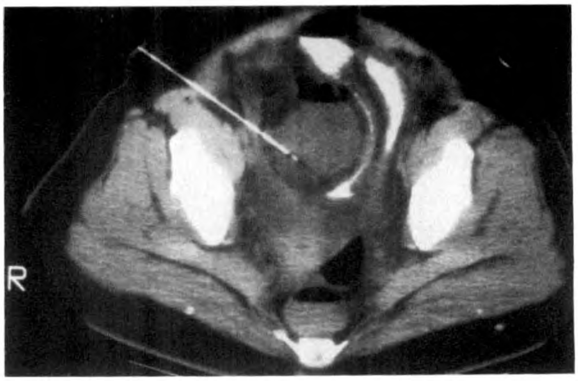


FIG. 5.

An axial section through a pelvic CT reveals a percutaneous aspiration needle with the tip in an abscess cavity associated with diverticulitis.

of CT in multiple interventional procedures has had great effect on the cost of medicine (Wittenberg et al, 1978). It has shortened the average hospital stay, as many diagnostic procedures can be performed on an out-patient basis. By providing pre-operative staging (Moss et al, 1981) (Fig. 4) and histological diagnosis through guided biopsy, CT is responsible for the elimination of exploratory surgery and a reduction in complications (Fig. 5). By eliminating surgery in advanced stages of cancer and permitting the earlier use of chemotherapy, CT has improved the quality of the remaining life for these patients (Fig. 6).

Magnetic resonance

Magnetic resonance imaging has made spectacular advances since its clinical introduction in 1981 (Alfidi et al, 1982; Buonanno et al, 1982; Crooks et al, 1982; Young et al, 1982). Its lack of harmful biological effects in the diagnostic range of radio frequencies, the ability to image directly in any plane (Fig. 7), obtaining simultaneous multiple tomographic slices and the greatly improved soft-tissue contrast resolution make it the most exciting diagnostic approach since the introduction of X rays in 1895. Adding to these the continuous improvements in spatial resolution with ever-improving coils (Fig. 8), ever thinner slices and new techniques for shortening scanning times makes MRI even more promising for the future (National Conference of State Legislators, 1985). The multiplicity of physical parameters that form the basis of proton MRI (proton density, T_1 and T_2 relaxation parameters, proton bulk motion, chemical shift, diffusion constants, magnetic susceptibility) afford endless opportunities for

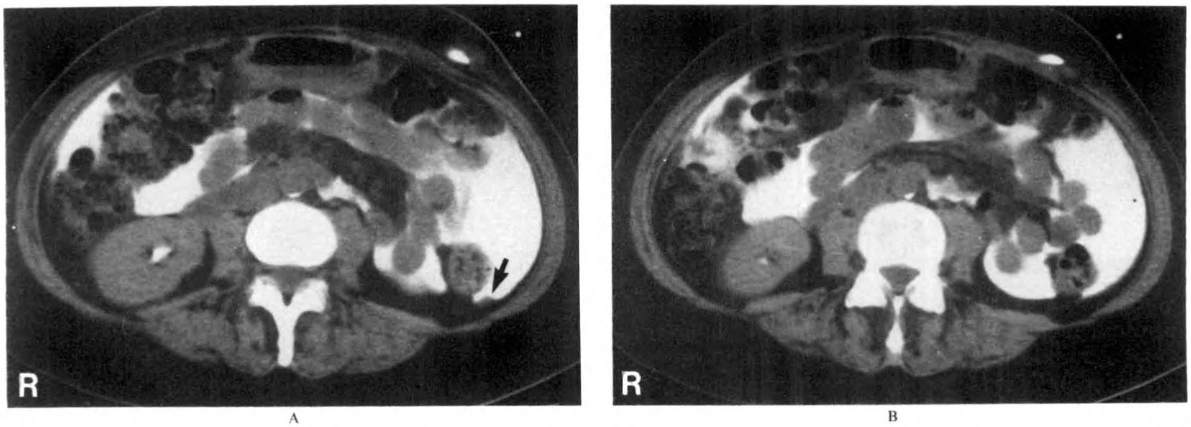


FIG. 6.

(A, B) Computed tomographic peritoneography exquisitely demonstrates a focus of residual tumour (arrow) in the (L) colic gutter in a patient with ovarian carcinoma receiving intraperitoneal chemotherapy.

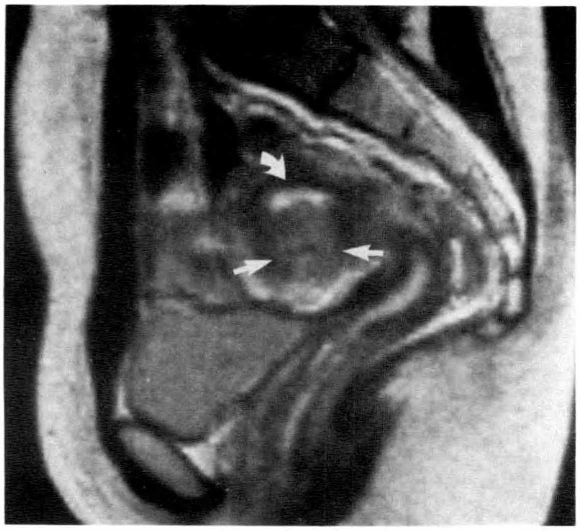


FIG. 7.
Sagittal section of a pelvic MRI scan demonstrates submucosal leiomyoma (arrows) and its relationship to the endometrial lining (curved arrow) (TR = 2.0, TE = 60).

their enhancement, improving the detection and characterisation of lesions (James & Margulis, 1983). As long as lesions have different physical MR parameters from normal tissues, they can be separated and made more distinct by the choice of a favourable technique. The addition of contrast media may further enhance the diagnostic capabilities of MRI (Brasch, 1983). Paramagnetic contrast media based on metabolic substrates or end-products can help follow normal and diagnose abnormal metabolic processes. Monoclonal antibodies made paramagnetic could identify precisely the nature of abnormal tissues. Other contrast media could evaluate perfusion and permit the precise quantification of blood flow.

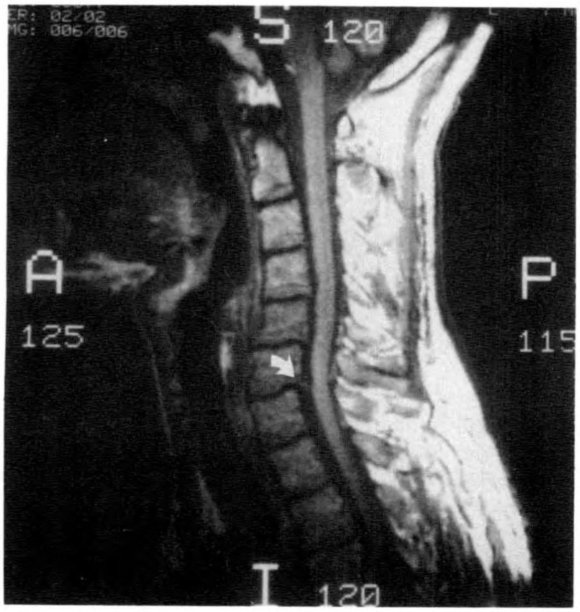


FIG. 8.
Cervical spine MRI examination using surface coil reveals outstanding spatial and contrast resolution. Note the protruded disk fragment in the subarachnoid space (arrow).

Magnetic resonance spectroscopy has been applied to the study of *in vivo* physiology with great success (Radda & Chulman, 1983). It promises better understanding of pathological physiology and clinical applications. So far, ^{31}P, proton and ^{13}C spectra have been studied. Localisation of the site of origin of the MR spectra from MR images has been rapidly advancing. Spectroscopic voxels of less than 1 cm^3 have been achieved (Luyten & den Hollander, 1983).

Interventional radiology

No field of radiology has affected the marriage of new technology with cost effectiveness and improvement of the patients' quality of life better than interventional radiology (Fig. 9). Angiography of coronary or peripheral arteries, the closure of arteriovenous malformations, the opening of occluded ducts, the drainage of abscesses, the removal of gallstones, biopsies of lesions, all depend on the combination of operator skill and sophisticated equipment resulting in non-invasive interventions at significant savings in cost. Other valuable side-effects are increased patient comfort, reduced number of complications and the possibility of the patients' earlier return to work. The savings from angioplasty, for example, are formidable (Doubilet & Abrams, 1984).

IMPROVEMENT IN COMMUNICATIONS

Radiology, even more than the rest of the health industry, has benefited from the large investments made by governments into defence and space explorations. As the budgets for these endeavours expand, talented engineers and physicists are attracted into them; when budgets shrink, many of these gifted workers move into medicine, bringing with them their skills in microcomputers, transmission of images over long distances with remarkable spatial resolution, telemetry, archiving and immediate retrieval of huge amounts of data in digital form. It is precisely these functions which are currently revolutionising departments of radiology. They make possible film-tracking transmission of images by telephone or radio, archiving and retrieval of digitised images (Fig. 10), transmission and checking of reports, handling of financial and personnel data and financial control (Allman et al, 1983; Curtis et al, 1983). Many of these functions still need to be perfected and integrated into larger health-centre systems, but the basic capabilities are present. When these difficulties are resolved the results will be further shortening of patient hospital stays, saving of physicians' time with greater

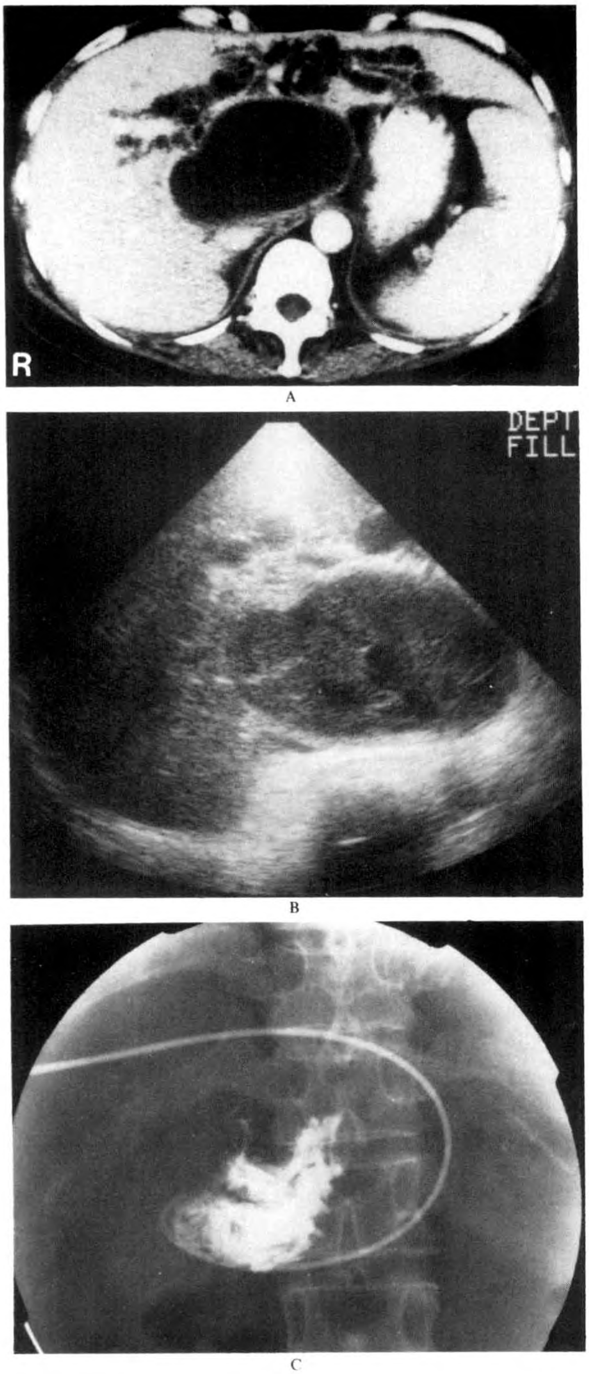


FIG. 9.

(A) A CT scan shows a massive hepatic cyst extending off the caudate lobe of the liver into the lesser sac in a patient with adult polycystic disease. (B) The ultrasonogram demonstrates the complex nature of this abscess and the real-time capability enabled the interventional radiologist to place a percutaneous transhepatic drain into the abscess (C). The tube was pulled 8 days later. The patient was saved a surgical procedure.

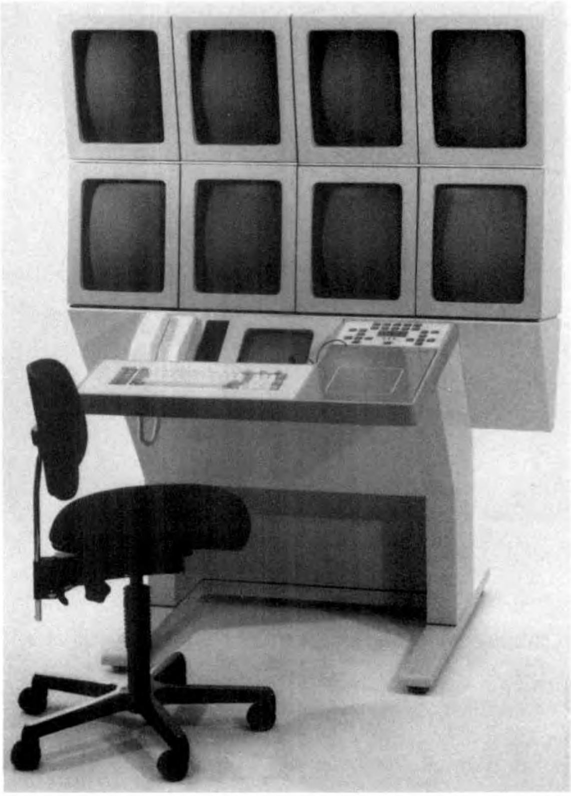


FIG. 10.

Photograph of a system for digital archiving and display of radiographs (Raytel Labs, 1004 Stewart Drive, Sunnyvale, CA 94086, USA).

efficiency of clerical help and reduction in the number of people currently required to run a highly cumbersome system. Digitised image acquisition, transmission and archiving may reserve the use of halogen films only to multiformat images obtained from digital data, which can then be viewed and compared on film alternators. Multimonitor viewers will probably be too expensive to be disseminated throughout the many sites needed in a modern medical centre.

Integration of modalities

The tremendous advances in technology resulting in the new, less invasive modalities can produce economic benefits if an integrated system is developed. Algorithms for their logical and sequential employment must, however, be developed, reviewed and updated at frequent intervals. Communication between radiologists and their other clinical colleagues must be continuously maintained through conferences and rounds. A system for the development and use of expensive and complicated equipment must be devised which will enhance economy and efficiency.

Thus used, technology will have achieved its purpose.

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Book reviews

Induction of Thyroid Cancer by Ionizing Radiation. National Council on Radiation Protection and Measurements, Report No. 80, pp. viii+93, 1985 (NCRP, Bethesda, USA), $13.00.
ISBN 0-913392-72-3

Official reports often do not receive the attention in the scientific literature that they deserve. This little report from the NCRP is, in fact, a very good review and summary of the evidence in man of radiation carcinogenesis in the thyroid. It begins by developing a risk-estimate model, allowing for a minimum induction period of 5 years and for a subsequent lifetime risk dependent on life expectancy. Thyroid cancer after external radiation exposure is studied next, and an arbitrary decision is made that cell killing will be dominant over carcinogenesis at doses over 1500 rad and, therefore, ruling out treatment of thyrotoxicosis, lymphoma or carcinoma.

The extensive North American experience of X-ray treatment in childhood for benign disease is the first main source of study, together with more recent investigation, especially in Israel, of patients having had X-ray therapy to the scalp for tinea.

Evidence from Japanese atomic-bomb survivors follows. Effects of age, sex and race are considered. Human experience after exposure to iodine 131 is then described, with essentially negative results, in fact a deficiency. It is concluded simply that ^{131}I is less carcinogenic (rad for rad) than external radiation. The high rad doses from ^{131}I and the dominance of cell killing are not discussed.

Animal data follow and the extensive literature is factually summarised. There is then much description of the very limited work done with iodine 125, and of the even sparser data on iodine 129, technetium 99m and iodine 123. The physical peculiarities of the radiation from these nuclides are well described and explained.

Finally, a numerical model is constructed. This gives a very good estimate of the absolute risk using age and sex factors and even lethality. There is still room for more discussion, however, on what is called the "dose effectiveness reduction factor", *i.e.*, taking the effectiveness per rad from external radiation and iodine 132, iodine 133 and iodine 135 to be 1, but only ⅓ for iodine 131 and iodine 125.

Altogether, this is an extremely good review of a complex and very interesting topic; it contains virtually all the relevant evidence.

Keith E. Halnan

Recent Developments in Digital Imaging. Ed. by K. Doi, L. Lanzi and P.-J. P. Lin, pp. vii+576, 1985 (American Institute of Physics), $60.00 ($40.00 members).
ISBN 0-88318-463-X

Digital radiography as a subject area is beginning to show rapid growth, and this book is an indication of this. It presents the proceedings of a summer school held in 1984 and organised by the American Association of Physicists in Medicine. Thirty papers were presented at the meeting by experts in the field and these represent 576 pages of text.

The book falls naturally into three parts. The first part, comprising six chapters, consists of the general background physics of imaging and imaging systems with attempts to match this to the digital format. The second part, of 10 chapters, deals with technology, at present under development or actually undergoing clinical evaluation, for digital radiographic application. There is a strong film-replacement undercurrent to this section which covers many of the existing leading contenders for this role. The final part, of 14 chapters, deals mainly with digital subtraction angiography and covers data, including image processing, as well as equipment evaluation technique.

The book is well presented, even allowing for the variations in type face, with each paper providing a comprehensive bibliography. The book will appeal mainly to scientists interested in digital medical imaging and gives an up to date scientific and technical background to this field.

B. M. Moores

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Transcatheter embolisation of arterial aneurysms

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ABSTRACT

Eleven cases of bleeding aneurysms and pseudoaneurysms, with and without arterio-venous fistula, involving different vascular territories were treated by transcatheter embolisation and the results are reported. Gelfoam was used in two cases and steel coils in the remaining nine cases. Embolisation by the steel-coil technique proved to be very efficient. The experience in these 11 cases shows that it is usually not necessary to embolise the aneurysm cavity but simply to occlude the feeding proximal vessel, consequently sparing the weak aneurysmic wall the risk of rupture and allowing the aneurysms to clot as a result of reduced or occluded blood flow.

Arterial aneurysms and pseudoaneurysms may be congenital, atherosclerotic, related to trauma, surgical procedures or may be secondary to necrosis of the arterial wall as a result of inflammation, chemical digestion or radiation arteritis. Almost any artery may be affected, regardless of location and function. Surgery has been the usual treatment of choice but in some cases the surgical approach is difficult and cumbersome, leading to extensive organ ablation. Transcatheter therapeutic occlusion is now a well accepted alternative technique and is effective in a wide range of clinical situations (Castaneda-Zuniga et al, 1976, Katzen et al, 1976; Wallace et al, 1976; Richman et al, 1977; Cho & Stanley, 1978; Wallace et al, 1978; Higgins et al, 1979; Nakamura et al, 1981; Uflacker et al, 1983), although there are few reports of transcatheter embolisation in the treatment of arterial aneurysms and pseudoaneurysms (Chang et al, 1978; Rosen et al, 1978; Lina et al, 1979; Mathisen et al, 1982; Uflacker & Diehl, 1982; Uflacker & Saadi, 1982). Embolisation proved to be a safe and effective method of treatment and obviated some otherwise difficult surgical procedures. Arterial pseudoaneurysms may be isolated or connected to an arterio-venous fistula, features which slightly modify the embolisation approach. We present 11 cases of aneurysms and pseudoaneurysms, with and without arterio-venous fistula, treated by transcatheter embolisation.

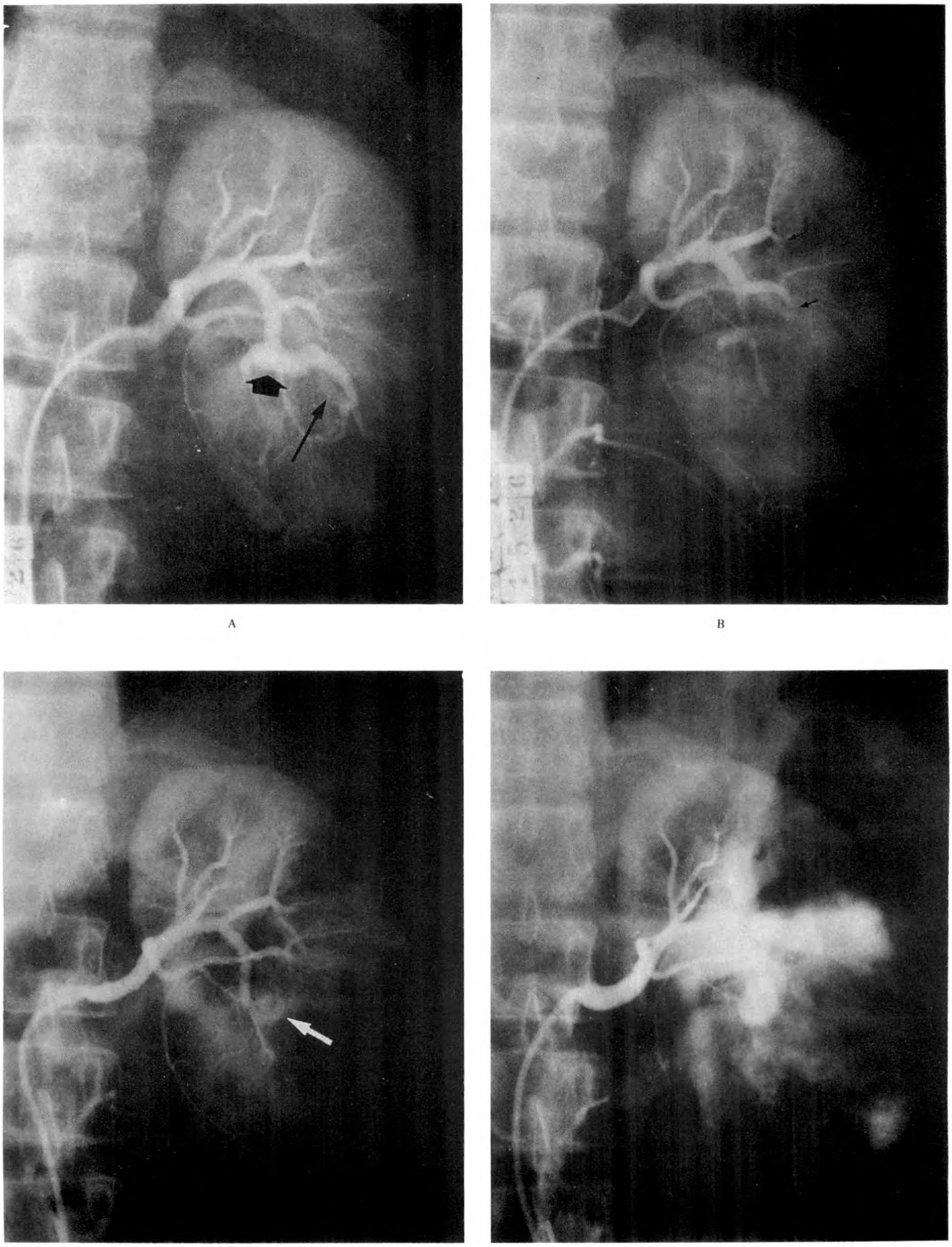
MATERIAL AND METHODS

Eleven cases of bleeding aneurysms and pseudoaneurysms with arterio-venous fistula (three cases) and without arterio-venous fistula (eight cases) were treated. Of these 11 cases, three involved the kidneys (Cases 1–3), one involved the internal carotid (Case 4) another two, the splenic artery (Cases 5 and 10); in Case 6 the pseudoaneurysm involved the superior mesenteric artery, another was in the right hepatic artery (Case 7) and one in a bronchial artery (Case 8). A further lesion was found in a femoro-popliteal venous bypass (Case 9) and in the remaining case a pseudoaneurysm was found

TABLE I

SUMMARY OF PATIENTS WITH ARTERIAL PSEUDOANEURYSMS

Case	Age (years)/ sex	Artery involved	Cause of pseudoaneurysm	Size of pseudoaneurysm (cm)	Arterio-venous fistula	No. of embolisations	Embolisation material	Results
1	22/M	Renal	Stab wound	1.0	Yes	2	Gelfoam	Nephrectomy
2	15/M	Renal	Blunt trauma	1.0	Yes	1	Coil	Good
3	23/M	Renal	Surgery	1.5	No	2	Coil	Nephrectomy
4	38/M	Carotid	Radiotherapy	1.5	No	1	Coil	Good
5	44/M	Splenic	Necrotising pancreatitis	2.0	No	1	Coil	Good
6	41/M	Superior mesenteric	Surgery	1.0	Yes	1	Coil	Good
7	58/M	Hepatic	Rheumatic disease	2.0	No	1	Coil	Good
8	44/F	Bronchial	Tuberculosis	1.5	No	1	Gelfoam	Good
9	58/F	Femoro-popliteal bypass	Surgery	5.0	No	1	Coil	Good
10	61/F	Splenic	Atherosclerosis	5.0	No	1	Coil	Good + surgery
11	28/M	Internal maxillary	Trauma Le Fort III	2.0 0.5	No	2, bilateral	Coil + Gelfoam.	Good



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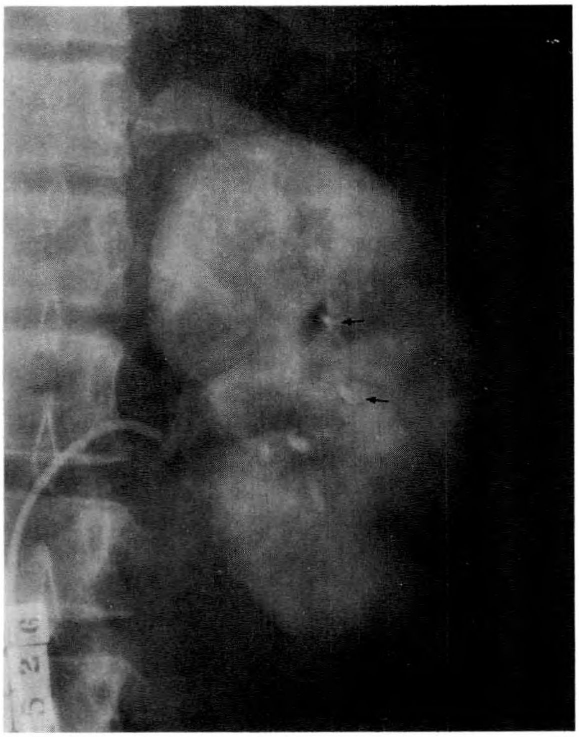

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FIG. 1. *Case 1.*

(A) Selective left renal arteriogram demonstrating a traumatic renal pseudoaneurysm (short arrow) and an arterio-venous fistula with early venous filling (long arrow). (B) Post-embolisation angiogram showing a pseudoaneurysm occlusion and unintentional embolisation of normal renal branches (small arrows). (C) Late-phase angiogram showing the Gelfoam fragments at normal branches (small arrows). (D) Follow-up angiogram showing recurrent bleeding (white arrow). (E) Post-embolisation angiogram demonstrating occlusion of the segmental branch, close to the main renal artery.

in the internal maxillary artery (Case 11). In three of the 11 cases, the lesion was related to a previous surgical procedure. A fourth case was secondary to blunt trauma, another to a stab wound, one was radiation-induced, another two were probably inflammatory and in the remaining cases the lesions were related to necrotising pancreatitis and facial trauma. Two of these cases (5 and 6) have been reported by us previously (Uflacker & Diehl, 1982; Uflacker & Saadi, 1982). Case 10 was atherosclerotic.

In two cases Gelfoam (Upjohn Co., Kalamazoo, Michigan) was used for embolisation, while in the remaining cases steel coils were used, except for one case where both Gelfoam and coils were used (Table I).

REPRESENTATIVE CASE REPORTS

Case 1 (Fig. 1)

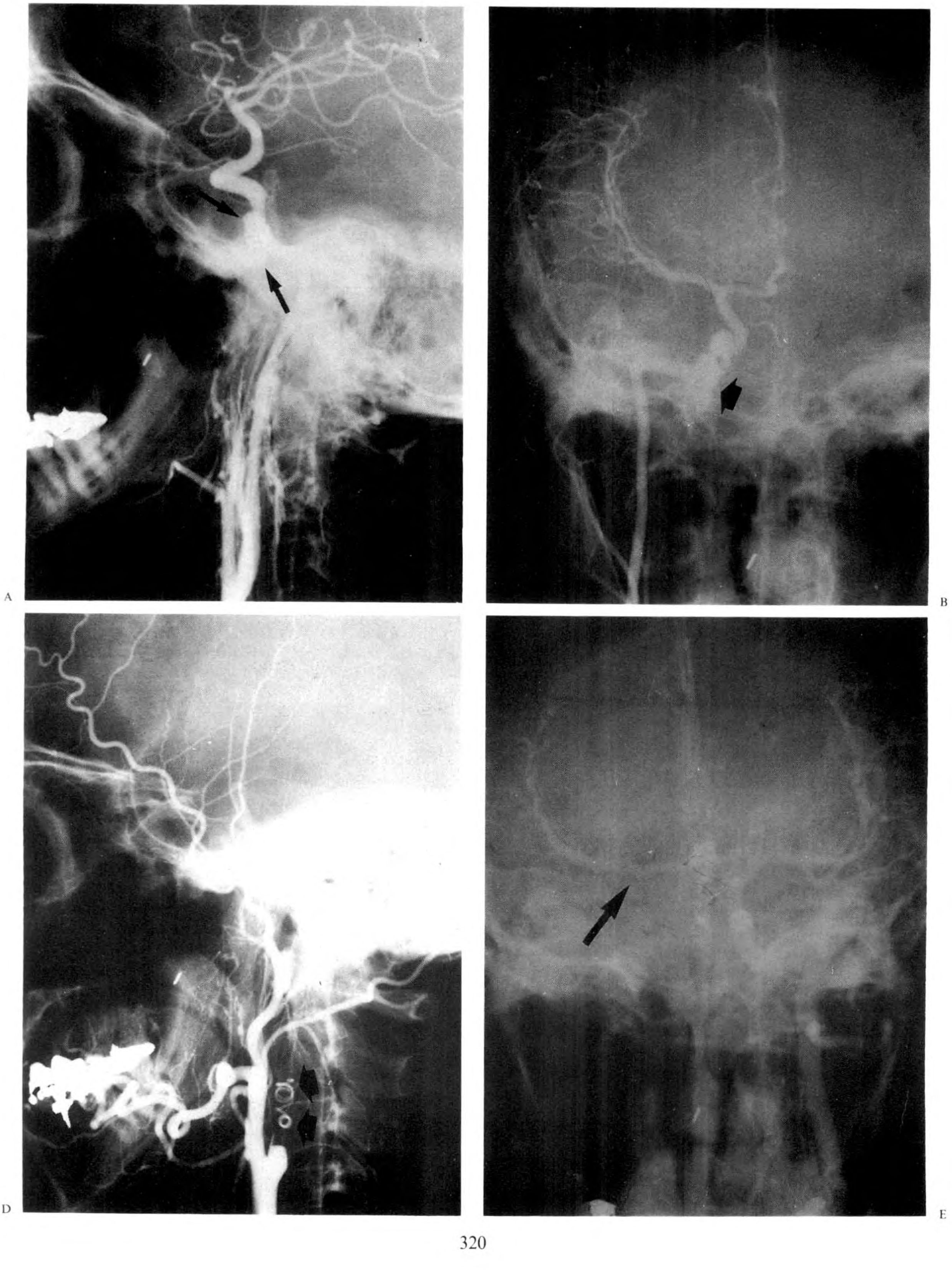
A 22-year-old male was stabbed in the back with resulting massive haematuria and shock. Emergency surgery at another hospital disclosed a laceration of the lower pole of the left kidney which was repaired by primary anterior and posterior suture. Haematuria persisted and 2 days after surgery a renal angiogram showed laceration of the lower pole of the left kidney. One week after injury the patient was transferred to our institution with increasing haematuria, requiring blood replacement and with severe back pain. Urography showed extensive filling defects in the left calyceal system with markedly retarded excretion. Selective left renal arteriography disclosed a pseudoaneurysm with arterio-venous fistula at the lower pole of the kidney, with active bleeding into the renal pelvis. The segmental arterial branch related to the pseudoaneurysm was selectively catheterised and two Gelfoam pieces (4 mm × 10 mm) injected to occlude the artery. Control angiography confirmed the segmental artery occlusion but some fragmentation of the Gelfoam pieces was noted, with consequent occlusion of normal renal artery branches. The haematuria and pain subsided during the next 4 days, without changes in blood pressure or white cell count. On the fourth day, however, haematuria recurred and repeat angiography was performed. The previously embolised vessels were still occluded but extravasation into the renal pelvis was detected and the segmental branch involved was completely occluded by Gelfoam. Haematuria decreased for 3 days but returned to the same level as before the second embolisation which had been followed by fever and a marked leucocytosis. Left nephrectomy was performed and a retroperitoneal haematoma drained. The patient improved after surgery and was discharged several days later.

Case 4 (Fig. 2)

A 38-year-old male was admitted with severe epistaxis. Four years before admission he had been treated with surgery and radiotherapy for a cylindroma of the right maxillary sinus with extension into the nasopharynx. The tumour had recurred in the nasopharynx 1 year before the current admission and had been treated again with radiotherapy. During the 4 months before the present admission the patient suffered frequent episodes of severe epistaxis, culminating on the morning before admission in a massive epistaxis with shock and marked decrease in the haematocrit. A few hours after admission there was recurrence of massive bleeding from the nasopharynx with shock necessitating transfusion of 3 l of blood in 1.5 h. A posterior nasal pack was attempted but proved ineffective. External carotid ligation was considered as an emergency measure, but it was decided to perform embolisation. Common right carotid angiography disclosed an internal carotid pseudoaneurysm at the level of the petrous bone, bleeding into the nasopharynx and sphenoid sinus. There was marked vasospasm of the external carotid artery branches. A contralateral carotid angiogram with cross compression demonstrated the patency of the anterior communicating artery. A 5 mm coil was delivered at the proximal part of the internal carotid artery followed by a 3 mm coil. The coils produced immediate occlusion with cessation of bleeding and no neurological sequelae were noted. One week later, right and left follow-up common carotid arteriograms demonstrated total occlusion of the right internal carotid up to the bifurcation, with normal circulation in the left internal carotid. The patient recovered uneventfully and was discharged a few days later without further bleeding. Two years after the procedure a brain abscess was drained but the patient died in the post-operative period.

Case 7 (Fig. 3)

A 58-year-old man was admitted with haematemesis and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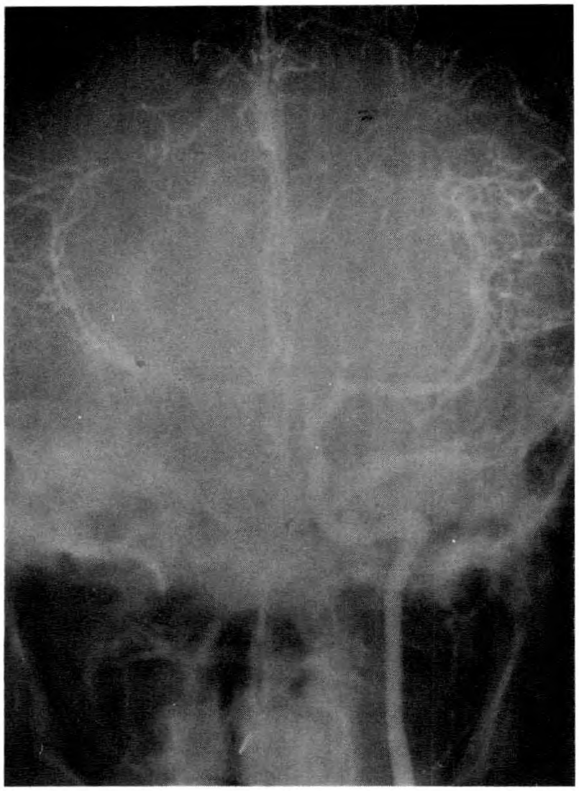

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FIG. 2. *Case 4.*

(A, B) A radiation-induced right internal carotid artery pseudoaneurysm is demonstrated on the lateral angiogram (arrows) with some active bleeding. (C) Contralateral carotid angiogram with right carotid compression showing permeability of the anterior communicating artery. (D) Follow-up angiogram demonstrating right internal carotid occlusion and the 5 mm and 3 mm coils in place (arrows). (E) Follow-up left carotid angiogram shows distal occlusion of the right internal carotid (arrow).

melaena. Seven years previously he had had an aortic valve replacement for rheumatic heart disease. Endoscopy showed the bleeding apparently originating in the duodenum but, at surgery, no abnormality was found in the stomach or duodenum. However, the gallbladder was full of blood and a diagnosis of haemobilia was made. Cholecystectomy was performed but examination of the gallblader revealed no abnormality. There was further massive haemorrhage on the eighth post-operative day and emergency surgical ligation of the proper hepatic artery was performed with control of the bleeding, although no cause for the bleeding was found. The patient recovered but remained anaemic. A hepatic arteriogram performed 2 weeks after the second operation demonstrated partial patency of the proper hepatic artery and filling of a 2 cm aneurysm of the right hepatic artery with multiple, perivascular, collateral channels. A 3 mm coil was placed selectively in the proper hepatic artery with total arterial occlusion and reduced filling of the aneurysm. The patient recovered uneventfully and control angiography 6 months after the embolisation showed no aneurysm, despite some degree of vascular recanalisation.

Case 10 (Fig. 4)

A 61-year-old woman was admitted because of abdominal pain and marked decrease in the haematocrit. Previous ultrasound examination, urography and retrograde pancreatography gave no abnormal findings. As the haematocrit remained lower than normal, vascular investigation was undertaken. Coeliac arteriography demonstrated a 5 cm aneurysm of the distal end of the splenic artery. Superselective catheterisation of the splenic artery enabled this to be occluded with a 5 mm coil. The control angiogram showed occlusion of the splenic artery with development of a collateral circulation through the left gastric artery with filling of distal splenic branches. The aneurysm remained filled by contrast medium. Following embolisation, the patient's condition improved, with increase in the haematocrit but, despite this, surgery was performed to ligate the splenic artery and the aneurysm was found to be thrombosed. Recovery was uneventful.

Case 11 (Fig. 5)

A 28-year-old man with a LeFort Type III facial fracture developed massive epistaxis following standard surgical treatment, despite the use of a posterior nasal pack. Hypotension developed rapidly and external carotid arteriography demonstrated a 2 cm pseudoaneurysm at the right internal maxillary artery which was embolised with Gelfoam particles and a 3 mm coil. The left internal maxillary artery was considered normal. On the following day epistaxis recurred and angiography confirmed occlusion of the right internal maxillary artery, but a 0.5 cm pseudoaneurysm was identified on the other side and the left internal maxillary artery was embolised with Gelfoam and a 3 mm coil. Bleeding was immediately controlled and recovery was uneventful.

DISCUSSION

Transcatheter embolisation is now a well established therapeutic technique and widely used in the control of bleeding of varying aetiology (Lea Thomas & Lamb, 1977; Rosen et al, 1978; Mathisen et al, 1982).

A large number of embolisation materials are now available for vessel occlusion (White et al, 1976; Greenfield, 1980), the choice of which depending upon the site and size of the vessel to be occluded, nature of vessel (artery or vein), the particular characteristics of the lesion, such as presence of an arterio-venous fistula, aneurysm or pseudoaneurysm, extent of vessel malformation, size of tumour and rate of bleeding. The choice will obviously also depend upon availability of the material within the institution.

Aneurysms of visceral arteries may be difficult to treat surgically and there is a high complication rate (Uflacker & Diehl, 1982); transcatheter embolisation is, therefore, a useful alternative. Pseudoaneurysms, because of their thin and weak walls, must be approached carefully on embolisation and low-pressure delivery systems used in order to avoid rupture (Lina et al, 1979; Greenfield, 1980; Uflacker & Diehl, 1982). Three main low-pressure techniques are currently available (Greenfield, 1980). The first is the injection of a liquid polymer, which can be introduced under very low pressure and provides instant occlusion (Kerber et al, 1977). The limitations of the fluid polymers are the risk of flowing-through of the polymer with failure

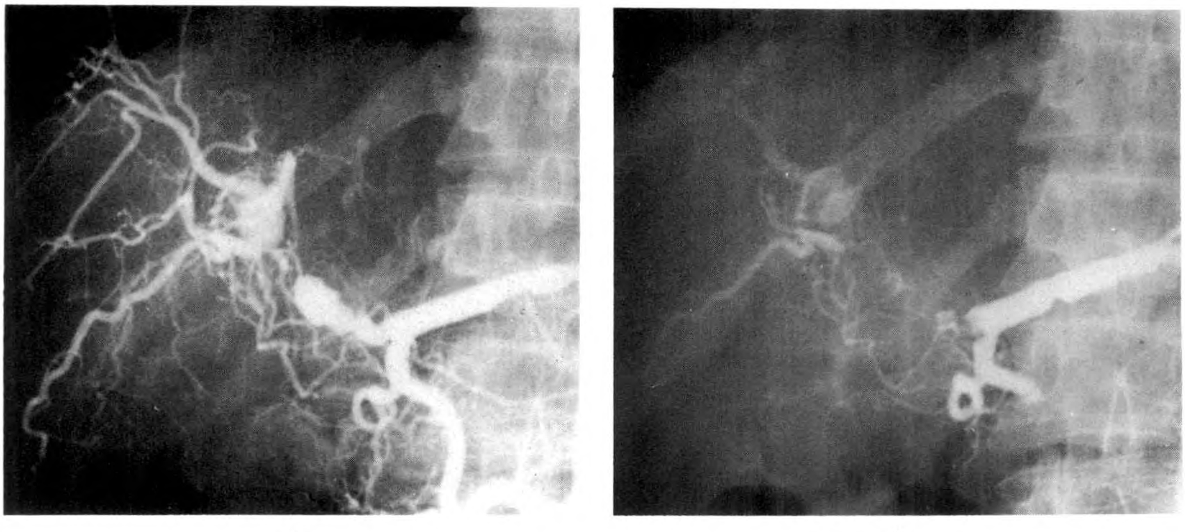

FIG. 3. *Case 7.*

(A) Common hepatic artery injection. Note the partially patent proper hepatic artery and fine collateral circulation, allowing some intrahepatic arterial flow and aneurysm patency. (B) Post-embolisation angiogram showing a reduction in intrahepatic arterial flow and incomplete filling of the aneurysm.

of distal occlusion as well as difficulty in handling the material. The second system is the use of mini-balloons flow-directed to the aneurysm mouth with immediate occlusion. The main limitation of this technique is the size of the vessel to be occluded. The use of the larger detachable balloons is restricted by the use of a larger catheter, which makes superselective catheterisation more difficult, much as with the older types of coil. The third system, the steel-coil technique, can be introduced without pressure rise in the vascular lesion. It has few

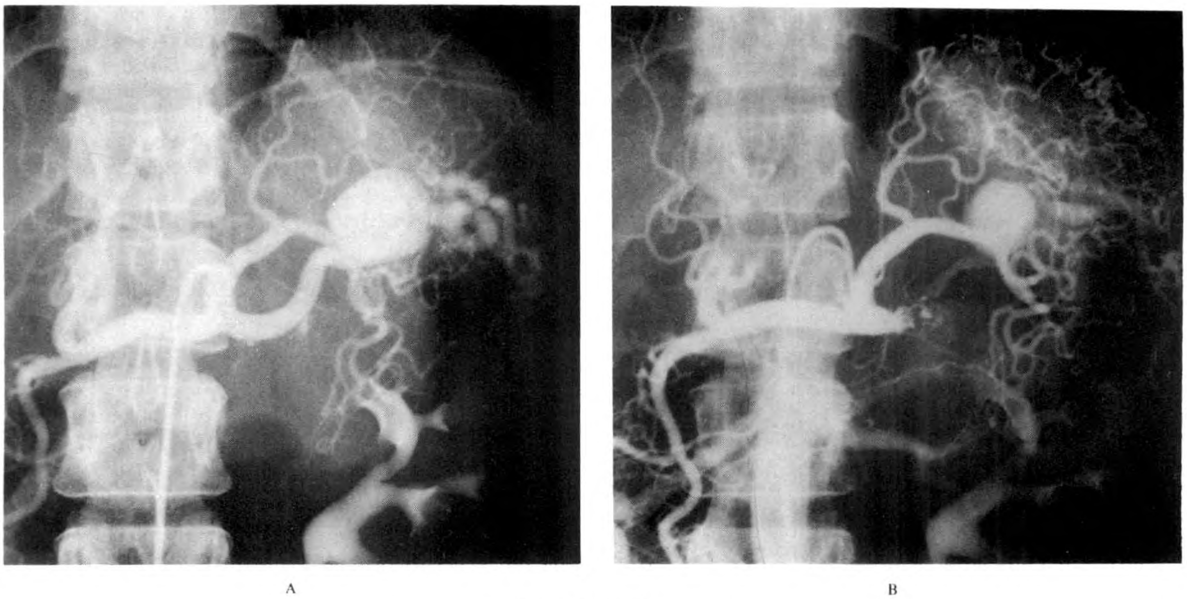

FIG. 4. *Case 10.*

(A) Coeliac angiogram demonstrates a 5 cm aneurysm at the splenic artery, with no evidence of bleeding. (B) Post-embolisation angiogram shows arterial occlusion but remaining contrast medium going into the aneurysm and collateral circulation through the left gastric artery.

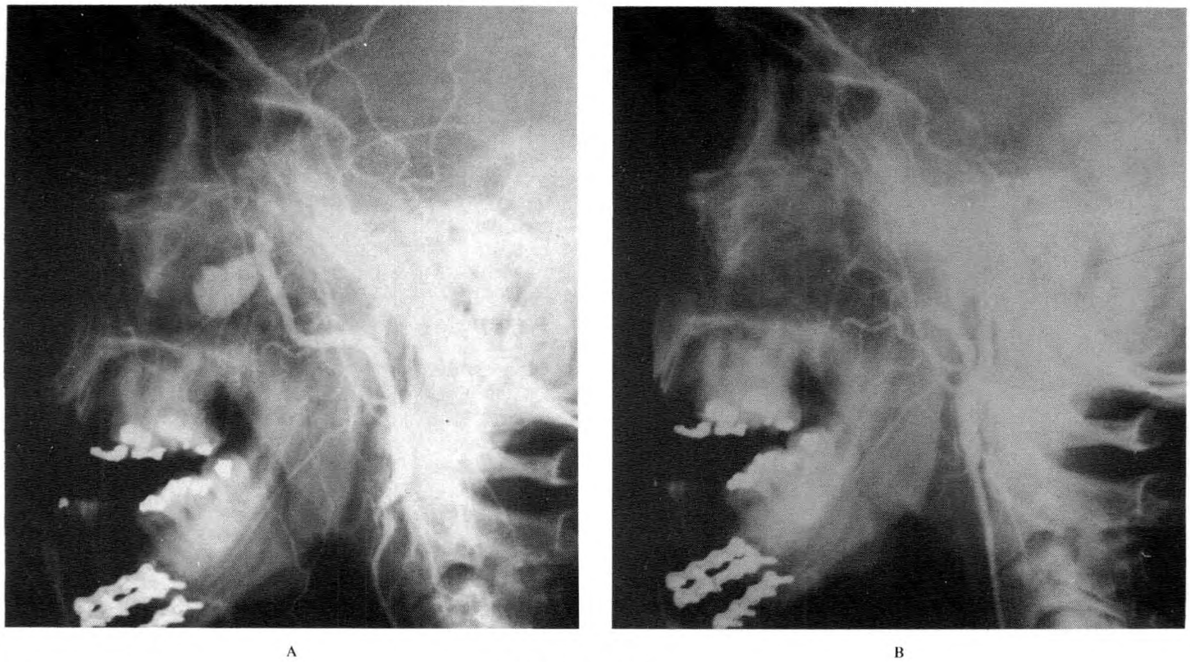

FIG. 5. *Case 11.*

(A) Right external carotid artery angiogram shows the pseudoaneurysm at the internal maxillary artery in a patient with facial trauma and posterior epistaxis. (B) After embolisation no filling of the aneurysm was obtained by contrast medium injection. Bleeding was controlled.

manipulation problems and is available in several sizes, allowing fine adjustment to the size of vessel to be embolised since it expands snugly against the vessel walls. The main limitation of the steel coil is the size of the vessel if there is a wide, high-flow arterio-venous fistula. In this case an additional spider device should be used to keep the coil in place.

Gelfoam embolisation may be useful for occlusion of small arterial aneurysms but, because of the risk of aneurysm wall rupture, due to increased intra-aneurysm pressure during injection, its use should be limited to special cases.

Our experience with the current 11 cases has shown that it is not necessary to embolise the aneurysm cavity but simply to occlude the feeding proximal vessel, consequently sparing the weak aneurysm wall and allowing clotting to occur from reduced or occluded blood flow. This is supported by recent reports of permanent occlusion of aneurysms and pseudoaneurysms by this technique (Kessler & Wholey, 1981; Uflacker & Diehl, 1982).

Our experience demonstrates the limited use of Gelfoam in intrarenal bleeding from an arterial pseudoaneurysm. Fragmentation of the Gelfoam with resulting ablation of normal kidney parenchyma limited its effectiveness and allowed bleeding from a proximal segment of the damaged artery. Even a second embolisation with Gelfoam controlled bleeding for only a short time and steel coils were found to be the most effective method in controlling traumatic renal bleeding (Uflacker et al, 1984).

One of our cases showed the rare situation of radiation-induced carotid rupture with pseudoaneurysm formation and massive nasopharyngeal bleeding. Vascular disease is, however, a well known complication of radiotherapy and includes atherosclerotic disease, aneurysm formation and vessel rupture from wall necrosis (Fajardo & Lee, 1975; Silverberg et al, 1978). Vessel rupture is an emergency situation with a high mortality rate and is most frequent in the carotid territory (Fajardo & Lee, 1975). Review of the literature indicates that most patients with large-vessel rupture after radiotherapy died (Fajardo & Lee, 1975). Our case was treated by coil embolisation during a dramatic episode of massive bleeding with minimal disturbance to the patient and immediate control of haemorrhage followed by thrombosis of the ruptured carotid artery and fast recovery of the patient. It was important to show the large anterior communicating artery, otherwise a temporary balloon catheter occlusion would have been desirable.

Surgical management of a bleeding hepatic artery aneurysm may pose problems because simple ligation of the hepatic artery is often inefficient in occluding the aneurysm or even in controlling bleeding, especially when located within the liver (Mathisen et al, 1982). Intrahepatic aneurysms should usually be treated by interventional angiography; surgical ligation of the proper hepatic artery or its branches should be reserved for cases of exsanguination from previously unsuspected aneurysms found at surgery (Mathisen et al, 1982).

Bronchial artery angiography and embolisation is a useful and reliable technique for control of massive haemoptysis (Uflacker et al, 1983).

Embolisation was a life-saving procedure in the case of traumatic epistaxis. Although internal maxillary artery embolisation has been performed to control epistaxis for some years (Roberson & Reardon, 1979), a traumatic lesion has rarely been described. Despite the need for a repeat procedure on the contralateral artery in our case, the embolisation was safe, effective and permanent.

It is our experience that, in cases of arterial aneurysm and pseudoaneurysm, the steel-coil technique occluding the proximal artery produces permanent occlusion in most cases and it is very seldom that a collateral circulation reopens the pseudoaneurysm cavity, despite recanalisation of the main artery by distal feeders (Uflacker et al, 1984).

Reduction of flow and pressure in the involved artery is frequently enough to control haemorrhage from the aneurysm or pseudoaneurysm and temporary balloon-catheter occlusion may also be useful in such cases. Steel coils are probably the safest and easiest material for aneurysm treatment in certain vascular areas. Detachable balloons are probably the second choice of treatment, while Gelfoam is felt to play only a limited role in the control of aneurysms.

Transcatheter embolisation should usually be attempted in cases of arterial aneurysm and pseudoaneurysm when the vascular bed is suitable and when surgical ligation is dangerous or difficult.

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Radionuclide venography: imaging monitor in deep-vein thrombosis of the pelvis and lower extremities*

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ABSTRACT

Seventy-four adults with documented deep-vein thrombosis of the pelvis and/or lower extremities had baseline and follow-up radionuclide venography (RNV), giving a total of 171 studies. Fifty-nine of the patients had unilateral venous thrombosis, of which 36 (61.0%) involved the left side and 23 (39.0%) the right. The higher incidence in the left side was attributed to the longer and more horizontal course of the left common iliac vein, as well as to compression by the right iliac artery and inguinal ligament. In 13 patients bilateral involvement was noted. "Normalisation" of the venous circulatory pattern was characterised by recanalisation and partial or significant disappearance of abnormal collaterals. This occurred in 43/74 patients. In 24 cases, no change was recorded during the interval, while seven patients deteriorated.

Deep-vein thrombosis of the pelvis and lower extremities may be documented by non-imaging and imaging methods (Barnes et al, 1976; Hayt et al, 1977; Kakar, 1977; Sy et al, 1978; Hull et al, 1981). Imaging methods include the use of a variety of radiopharmaceuticals such as $^{99}Tc^{m}$ MAA (Rosenthall, 1971), $^{99}Tc^{m}$ HAM (Webber et al, 1974), fibrinogen tagged with ^{123}I or ^{125}I (Henkin et al, 1974; Denardo & Denardo, 1977), radiolabelled streptokinase and urokinase (Charkes et al, 1975), $^{99}Tc^{m}$-labelled plasmin (Deacon et al, 1980) and large volume $^{99}Tc^{m}O_4^-$ (Sy et al, 1978) or contrast materials (Lea Thomas, 1982). The morbidity associated with contrast venography usually precludes its routine use as a monitoring technique after documentation of deep-vein thrombosis is established. This communication assesses the role of large volume $^{99}Tc^{m}O_4^-$ RNV technique as an imaging method in the monitoring of evolutionary changes in established deep-vein thrombosis of the pelvis and lower extremities. Scintigraphic changes in the baseline and sequential studies are correlated with the patients' clinical course.

TECHNIQUE

From August 1977 to December 1984, RNV, using the relatively diluted large volume $^{99}Tc^{m}O_4^-$ technique as described previously (Sy et al, 1978), was performed 1161 times on 998 adults in whom deep-vein thrombosis of the lower extremities and/or pelvis was clinically suspected. Radionuclide venography entailed the simultaneous injection, without tourniquets at the time of administration, into a dorsal vein of each foot of 8 mCi of $^{99}Tc^{m}O_4^-$ that was pre-diluted in 10 ml of normal saline. Three-second analogue dynamic images of the lower limbs and pelvis were obtained using a WFOV camera. Since the initial publication of the technique (Sy et al, 1978), a minor modification on the procedure had been made: if, during the dynamic portion of the study, the ipsilateral popliteal vein in a symptomatic limb was not visualised, reinjection (4 mCi of $^{99}Tc^{m}O_4^-$ pre-diluted in 5 ml of normal saline) in that limb was made, this time with a tourniquet tightly applied above the ankle joint.

Abnormal scintigraphic features indicated deep-vein thrombosis of the pelvis and/or lower extremities in 254 adults. Seventy-four of the 254 patients (26 men and 48 women, age range 18–87 years) had follow-up RNV at least once and sometimes up to four times, so that analysis of a total of 171 studies constitutes the basis for this report. The repeat studies were performed between 7 days and 3 years after the baseline study. In 55 of the 74 patients, however, the average interval between the baseline and the second study was only 18 days.

A wide-field-of view camera (15 in or 21 in crystal) equipped with a low-energy multipurpose collimator was used initially but from September 1980 to December 1984 all studies were performed on the 21 in-field-of-view camera.

RESULTS

Deep-vein thrombosis was demonstrated by initial RNV in 74 patients. A large majority (59) had unilateral venous thrombosis while 13 (18.1%) had bilateral involvement (Table I). Table II gives the side

TABLE I

DISTRIBUTION OF VENOUS THROMBOSIS IN 74 PATIENTS

Bilateral	13
Right	23
Left	36
Inferior vena cava	2

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TABLE II

SIDE AND SITES OF VENOUS THROMBOSES IN 74 PATIENTS

	Vein					Total
	Inferior vena cava	Iliac	Femoral	Popliteal	Great saphenous	
Right	–	22	16	16	1	55
Left	–	31	35	16	–	82
	5	–	–	–	–	5
Total	5	53	51	32	1	142

TABLE III

DISTRIBUTION OF VEINS OR COMBINATION OF VEINS INVOLVED IN 74 PATIENTS

Inferior vena cava only	2
Inferior vena cava and iliacs	3
Iliac, femoral and popliteal	10
Iliac and femoral	19
Iliac	9
Femoral and popliteal	10
Femoral	10
Popliteal	10
Greater saphenous	1
Total	74

and sites: 137 of 142 identifiable sites involved the iliac, femoral and popliteal veins, either singly or in combination. Table III indicates the vein involved. Combined iliac and femoral vein involvement (25.9%) is the most common. Interval changes on RNV are summarised in Table IV.

DISCUSSION

A significant majority of patients, 61.0% (36 out of 59), demonstrated deep-vein thrombosis of the left side only, which may be attributed to the anatomical differences between the two sides of the venous system. The left common iliac vein is slightly longer and more horizontal in its course than the right, and so may be more likely to be compressed by any existing pelvic mass or lesion. More importantly, the right iliac artery compresses the distal portion of the left common iliac vein, as does the inguinal ligament at the proximal portion of the left common iliac vein.

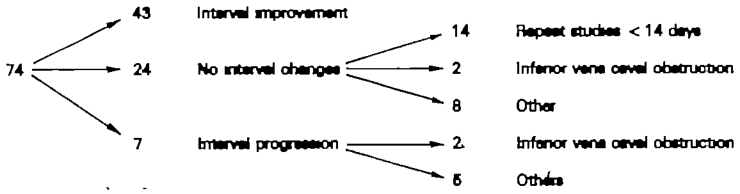
Recanalisation of thrombosed deep veins would be the optimum goal of anticoagulation or enzyme therapy. Scintigraphically, this improvement had been characterised by "normalisation" of venous circulatory pattern which is associated with significant disappearance of previously demonstrable abnormal collaterals (Fig. 1). At times, however, there is no apparent recanalisation, except for significant disappearance of abnormal collaterals (Fig. 2). Occasionally, recanalisation is achieved, but residual collaterals remain near the occlusion site (Fig. 3). Such scintigraphic differences between examinations occurred usually within 14 to 21 days from the time of the baseline study. The 43 patients in this group showed commensurate clinical improvement in that swelling, discolouration and pain abated or disappeared.

In 24 patients, no improvement was identifiable on the follow-up studies although many of these patients showed similar clinical improvement. It is, however, known that a percentage of deep-vein thromboses will fail to recanalise, particularly if the thrombus is large and fully organised, and these patients may fall in this category, in which the developed collaterals take over the function of drainage. Fourteen of 24 patients in this group had repeat RNV performed after less than 14 days, hence there may have been later flow-pattern changes which were not scintigraphically documented.

In seven other patients who remained clinically unimproved, the scintigraphic changes were characterised by the development of more profuse and extensive collaterals and additional non-visualisation of previously patent veins and tributaries. Four of these seven had terminal carcinomatosis while a fifth had end-stage renal disease due to lupus erythematosus.

TABLE IV

SCINTIGRAPHIC INTERVAL CHANGES IN THE 74 PATIENTS


74
43 Interval improvement
24 No interval changes
14 Repeat studies < 14 days
2 Inferior vena caval obstruction
8 Other
7 Interval progression
2 Inferior vena caval obstruction
5 Others

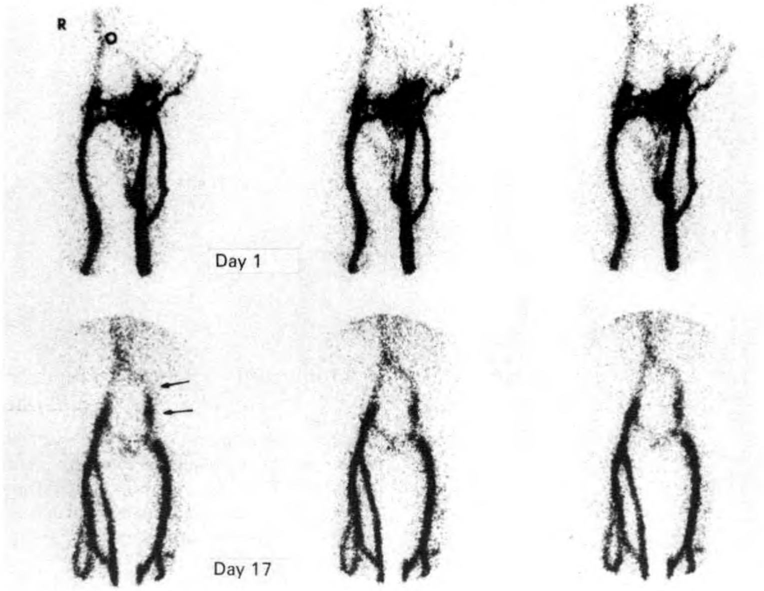


FIG. 1.
Three-second dynamic images of the pelvis and thigh showing recanalisation of the left common iliac and femoral veins (arrows) and disappearance of abnormal collaterals in 16 days following heparinisation. ○ indicates the umbilical level.

Two of the patients went on to develop inferior vena caval occlusion.

CONCLUSION

Based on the preceding data and experience, the authors recommend repeat RNV within 14 to 21 days following the initial scintigraphic diagnosis of deep-vein thrombosis.

Large volume $^{99}Tc^{m}O_4^-$ is an excellent imaging tool for the monitoring of deep-vein thrombosis of the pelvis and lower extremities, and is recommended specifically in these circumstances.

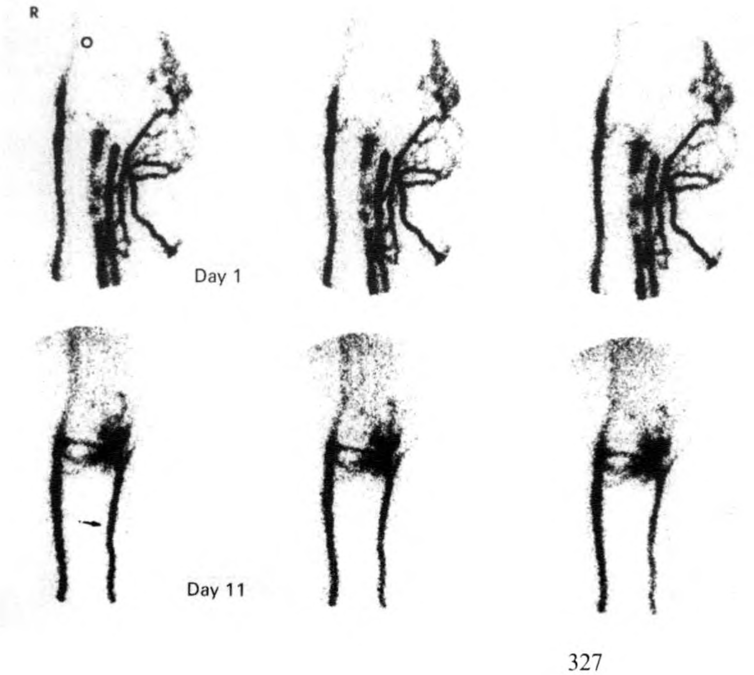


FIG. 2.
No apparent recanalisation of the left common iliac and femoral veins, although significant disappearance of collaterals was observed after 10 days. The more medially located great saphenous vein (arrow) remained patent. (Three-second dynamic images of the pelvis and thigh.)

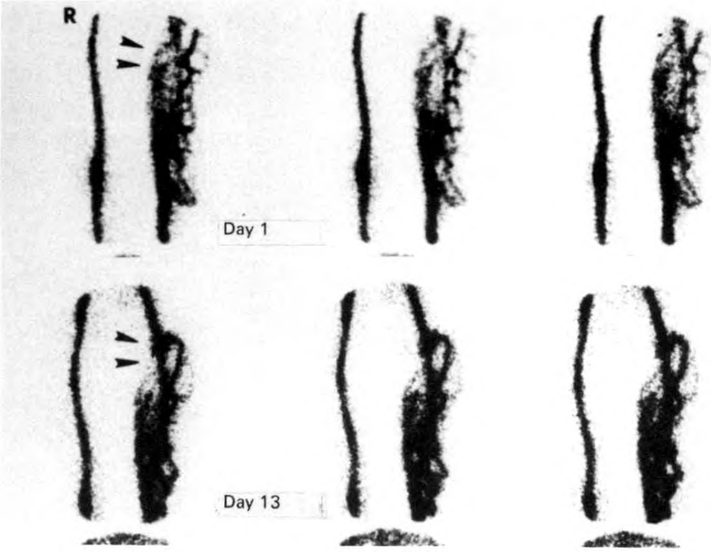


FIG. 3.

Evident recanalisation of left femoral vein (arrowheads) but residual collaterals still observed. This pattern was noted only rarely. (Three-second dynamic images of the thigh.)

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Intravenous digital subtraction angiography in patients with suspected bypass graft occlusion following surgery for peripheral vascular disease

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ABSTRACT

Intravenous digital subtraction angiography has been used to investigate 40 patients with suspected bypass graft occlusion. Its accuracy and clinical impact have been assessed.

Graft occlusion following surgery for peripheral vascular disease is a well recognised complication and vascular surgery is itself now commonplace. Intravenous DSA, because of its simplicity, readily lends itself to the investigation of this problem. We have reviewed the results in 40 patients studied at the Manchester Royal Infirmary over 2 years, and have considered the impact of intravenous DSA in terms of its accuracy and its effect on clinical management.

PATIENTS AND METHOD

Between January 1983 and January 1985 (soon after intravenous DSA had become available) 40 patients (29 males and 11 females; age range 47–86 years) with suspected peripheral vascular bypass graft occlusion underwent intravenous DSA at times ranging from less than 24 h to 11 months following the original graft insertion. Operative details are given in Table I. A total of 44 angiographic studies were performed for separate occlusive episodes. Doppler ultrasound was not employed to any extent.

An International General Electric IGE LUA Fluoricon 3000 digital system, which has a maximum field size of 23 cm but no table movement, was used. Because of this constraint on field size it was necessary to deliver contrast medium in a number of separate injections. A non-ionic, low osmolar agent (iohexol) was administered via a short 16 G cannula into an antecubital vein.

RESULTS

Nine of the 44 studies were carried out in the first post-operative week. Of these nine, the clinical diagnosis was incorrect in four instances (44%). Of the 35 studies performed after this time, only two were clinically misdiagnosed (6%).

In five of the six instances of misdiagnosis, intravenous DSA showed grafts to be patent which had been thought to be occluded. In the one remaining case a femoro-popliteal bypass graft was thought patent, but was shown angiographically to be occluded with very good collateral flow through the profunda femoris artery. In no case was there an angiographically occluded graft which was shown to be patent at subsequent surgery.

Conventional angiography was required following intravenous DSA in five cases, and these occurred between 6 weeks and 11 months after surgery. In four of these five cases there was uncertainty about the "run-off" (popliteal and tibial arterial anatomy) and there was one technical failure. No lesions amenable to angioplasty were found with intravenous DSA, hence this did not influence the decision to undertake conventional angiography.

DISCUSSION

Intravenous DSA has become the investigation of choice at our institution for patients with suspected vascular bypass graft occlusion. As has been found in a previous study (Pond et al, 1982) it has proved completely reliable in determining graft status, and our experience has shown that, particularly when undertaken in the early post-operative period, it can reverse a clinical impression. During the first week following surgery, soft-tissue swelling may make examination of

TABLE I

OPERATIVE DETAILS

Graft types	Number
Femoro-distal	29
Aortic bifurcation	4
Femoro-distal and aortic bifurcation	2
Axillo-femoral	2
Others	3
Total	40

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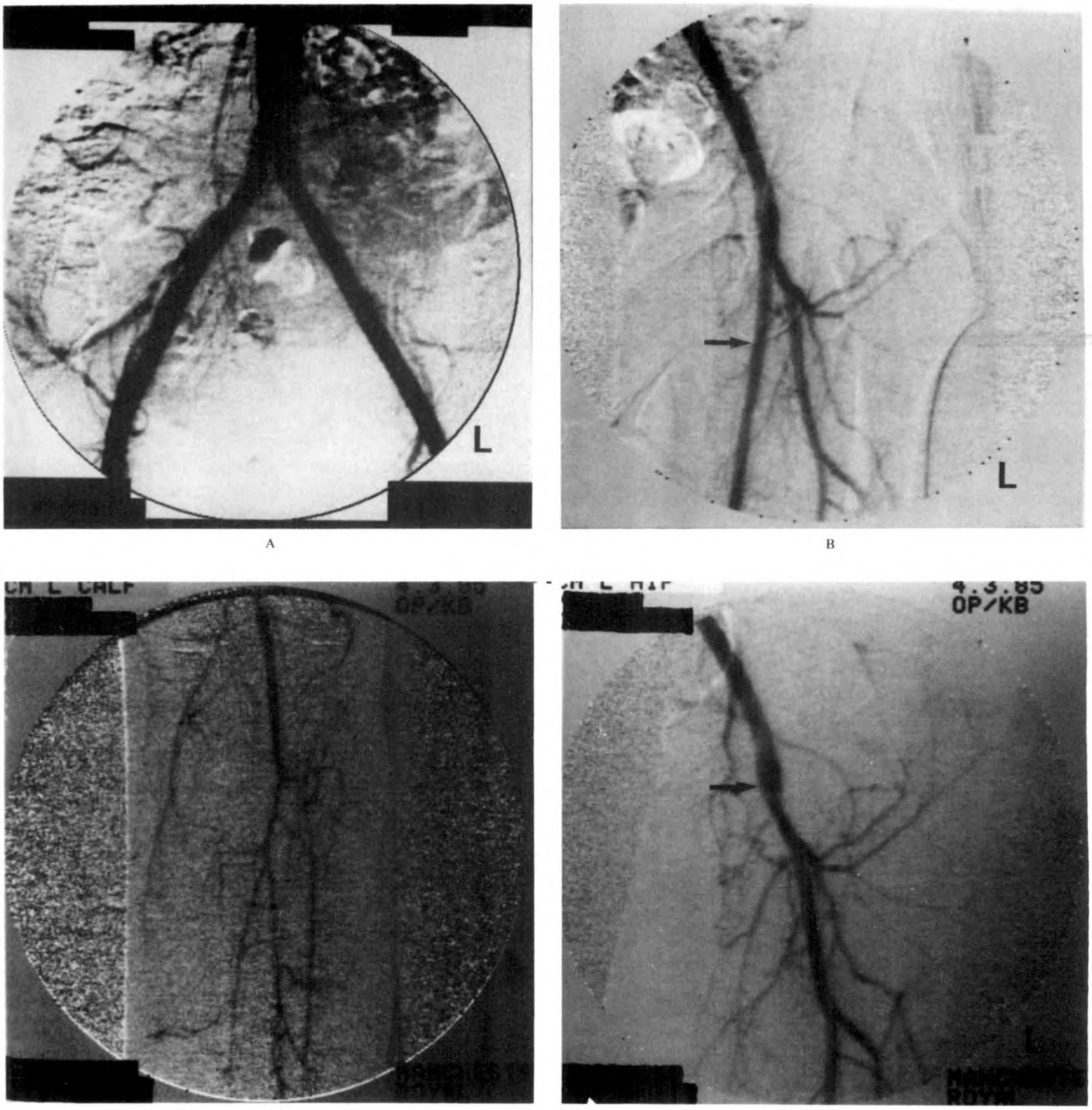

A B C D

FIG. 1.

Patient C.M., intravenous DSA. (A) A patent aortic bifurcation graft is shown. (B) The proximal part of a coexisting, femoro-popliteal bypass graft is patent (arrow). (C) There is good run-off into the popliteal and tibial arteries. (D) Same projection as B, repeat study at an interval of 7 months. The femoro-popliteal graft is now occluded at its origin (arrow).

lower-limb pulses difficult. The simplicity of intravenous DSA and its accuracy in regard to graft status, irrespective of time after surgery, circumvent this difficulty. The early post-operative patient can be examined with little upset and repeat studies are readily undertaken using the technique (Fig. 1), and it is also versatile (Fig. 2). With an antecubital route for contrast-medium delivery, the complication rate is virtually that of the contrast medium used, and hazards related to arterial or graft puncture are avoided. Patient immobility is an important consideration during image acquisition, and because there is a rapid delivery of

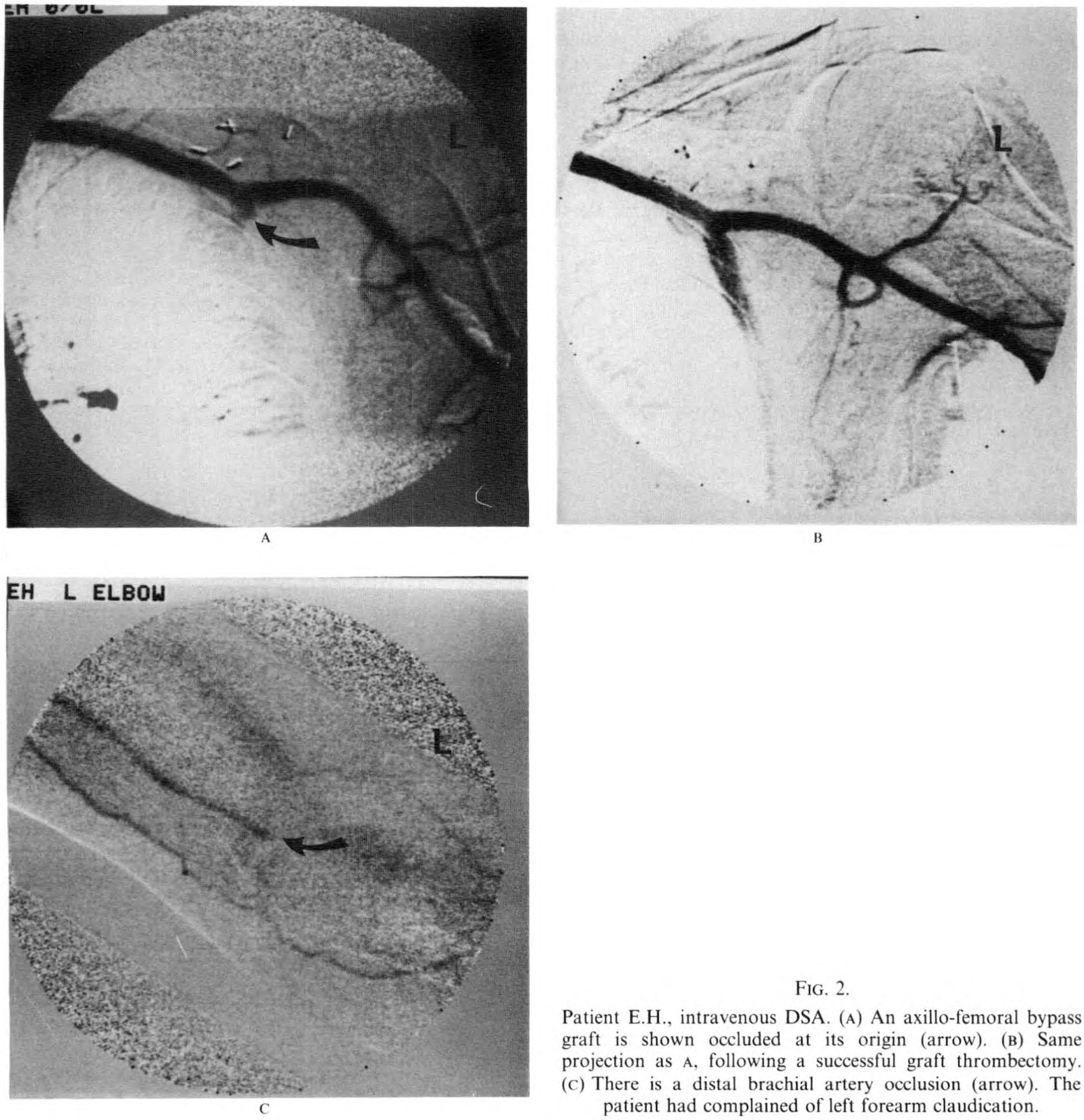

FIG. 2.

Patient E.H., intravenous DSA. (A) An axillo-femoral bypass graft is shown occluded at its origin (arrow). (B) Same projection as A, following a successful graft thrombectomy. (C) There is a distal brachial artery occlusion (arrow). The patient had complained of left forearm claudication.

intravenous contrast medium a non-ionic, low osmolar agent, iohexol ("Omnipaque") is favoured, as this has been shown to produce less nausea than ionic media, even ioxaglate ("Hexabrix") (Foord et al, 1985).

Conventional angiography was required in a minority of patients and in all cases the occlusive episodes occurred some time after the original surgery. Excepting the one technical failure of intravenous DSA, the reason for further angiography was inadequate visualisation of the popliteal or tibial arteries. Soon after surgery the run-off is unlikely to have significantly altered from that demonstrated by the pre-operative (conventional) angiogram. This may not be the case with possible graft occlusion at a later stage following surgery, because of disease progression.

Failure to visualise arterial anatomy using intravenous DSA may be due to patient movement or poor left ventricular function, as well as to the presence of atheroma. Intravenous DSA may also over-estimate the extent of disease because of the limits on its power of image-resolution. There is then the possibility of a false positive diagnosis with respect to both the presence and extent of atheromatous disease, most importantly involving the popliteal and tibial arteries of those patients presenting with late graft occlusion.

In conclusion, we have found that intravenous DSA is an excellent means of investigating peripheral vascular bypass grafts and is particularly useful soon after surgery. A tailored approach to the imaging of these patients is possible, similar to that described by Kinnison et al (1984). Although still completely accurate regarding graft status, intravenous DSA may need to be complemented by conventional angiography, or indeed by intra-arterial DSA when some time has elapsed since the original surgery.

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Metastatic deposits from a previously treated carcinoma of the lung presenting as a renal cell carcinoma

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ABSTRACT

Two patients are presented who had each previously undergone resection of a primary lung carcinoma. They later developed the classical triad of loin pain, haematuria and an abdominal mass suggestive of a primary renal tumour. Investigations, including intravenous urography, ultrasound and renal arteriography, supported the diagnosis. However, at operation both patients had para-aortic lymph node metastases from the lung carcinoma surrounding the renal pedicle and invading the renal parenchyma. It is suggested that further investigations might allow pre-operative diagnosis and thus avoid the need for surgery in such patients.

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The first patient, a 53-year-old man, a life-long heavy smoker, presented with 2 months' history of progressive

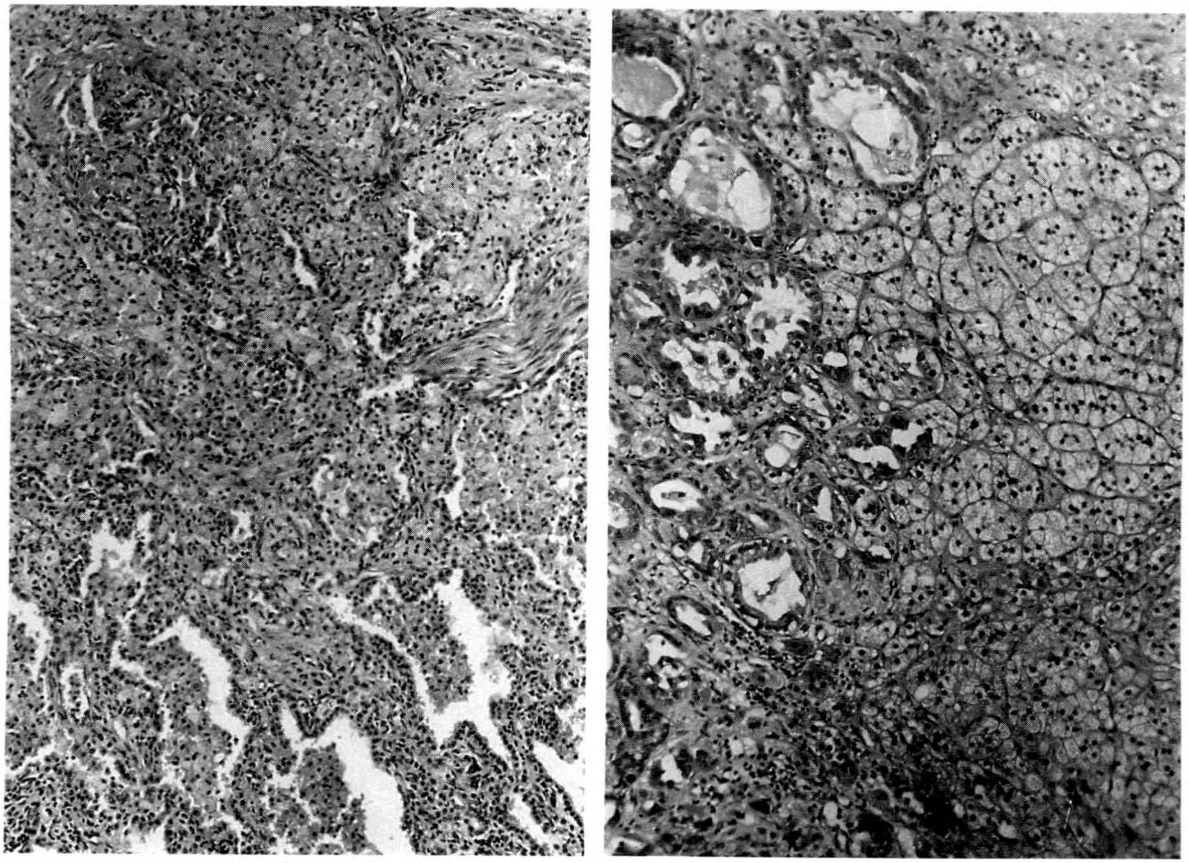

FIG. 1.

Case 1. Histology of the primary lung tumour (A) and the secondary renal tumour (B). The lung tumour shows glandular and squamous differentiation typical of an adeno-squamous "scar" carcinoma. The renal mass shows infiltration by a poorly differentiated squamous-cell carcinoma similar to the lung tumour and consistent with metastases from the lung to the kidney. H & E × 170.

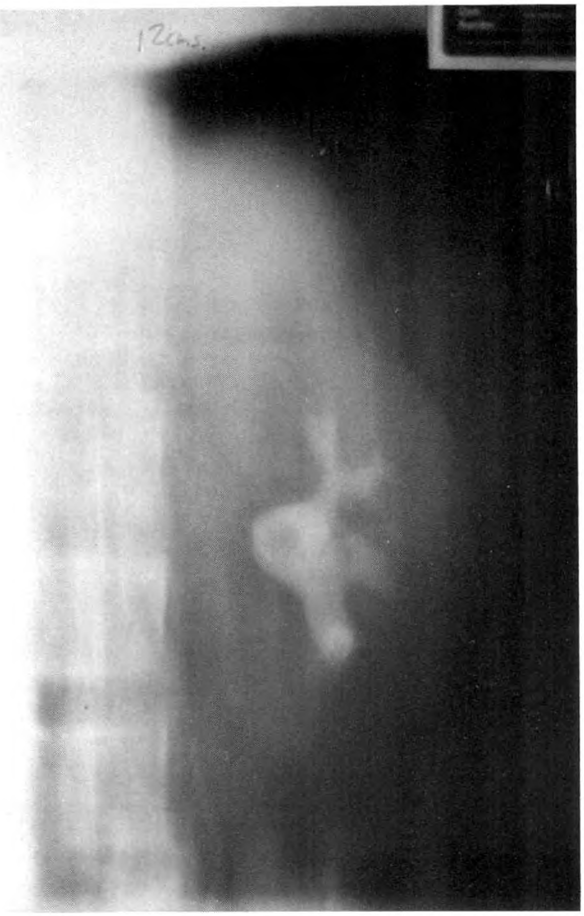

FIG. 2.

Case 1. Intravenous urogram showing filling defect in left renal pelvis and vertical alignment of this kidney.

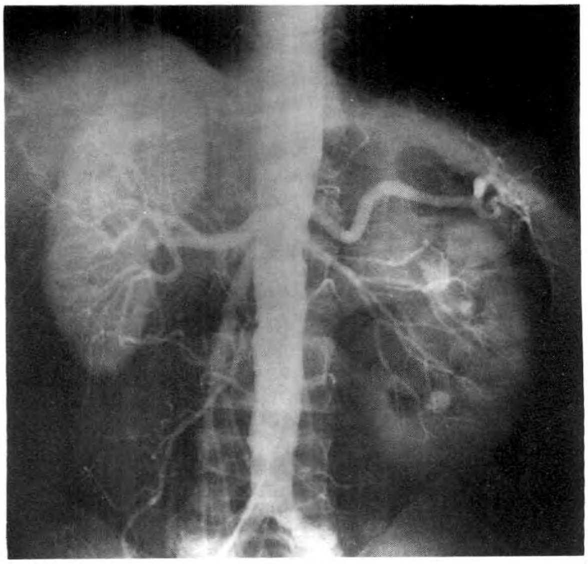

FIG. 3.

Case 1. Renal arteriogram showing elongated encased left renal artery.

shortness of breath and haemoptysis. A chest radiograph showed an area of collapse and consolidation of the apex of the right lung. He underwent bronchoscopy and right upper lobectomy and made an uneventful recovery. Histology showed the lesion to be an adeno-squamous carcinoma involving the right upper lobe (Fig. 1). There was no lymphatic involvement.

Four years later, he underwent cholecystectomy for gallstones, when a thickened pancreas was noted but no other intra-abdominal pathology could be demonstrated. He remained well for a further 14 months, when he developed total painless haematuria and left loin pain. On examination a 10 cm × 14 cm mass was palpable bimanually to the left of the mid-line above the umbilicus. The mass appeared to move with respiration.

Intravenous urography was performed (Fig. 2) and the left renal pelvis contained a 1 cm diameter filling defect. Renal ultrasound showed a mass in the left hilum, with a full pelvis containing abnormal echoes. Renal arteriography (Fig. 3) showed an elongated, narrowed and encased left renal artery.

No pathological circulation was noted. There was a soft-tissue mass contiguous with the pelvis displacing the kidney laterally. The renal vein was not visualised. Cystoscopy revealed no lesion within the bladder and so, on the basis of the clinical signs and symptoms and the radiographic findings, the left kidney was explored via a loin incision. The kidney was found to be oedematous and haemorrhagic, displaced downwards and laterally by a mass of glands encasing the renal pedicle and invading the renal substance. The mass was not resectable; biopsies were taken and the wound closed. The biopsies showed lymphatic deposits containing adeno-squamous carcinoma from a primary lung carcinoma (Fig. 1). The patient declined further treatment and died 3 months later.

The second patient, a 65-year-old lady, a heavy smoker, developed progressive shortness of breath 2 months before admission to hospital. A chest radiograph showed an opacity in the left upper lobe and she was admitted for bronchoscopy and thoracotomy. She had a left upper lobectomy for a scar carcinoma showing both glandular and squamous differentiation (Fig. 4). No lymphatic metastases were seen and she made an uneventful recovery and remained well until 18 months later, when she developed pain in the left iliac fossa radiating to her back. She was noted to have heavy microscopic haematuria and a palpable mass 10 cm in diameter in the region of the left kidney. Chest radiography showed only the previous upper

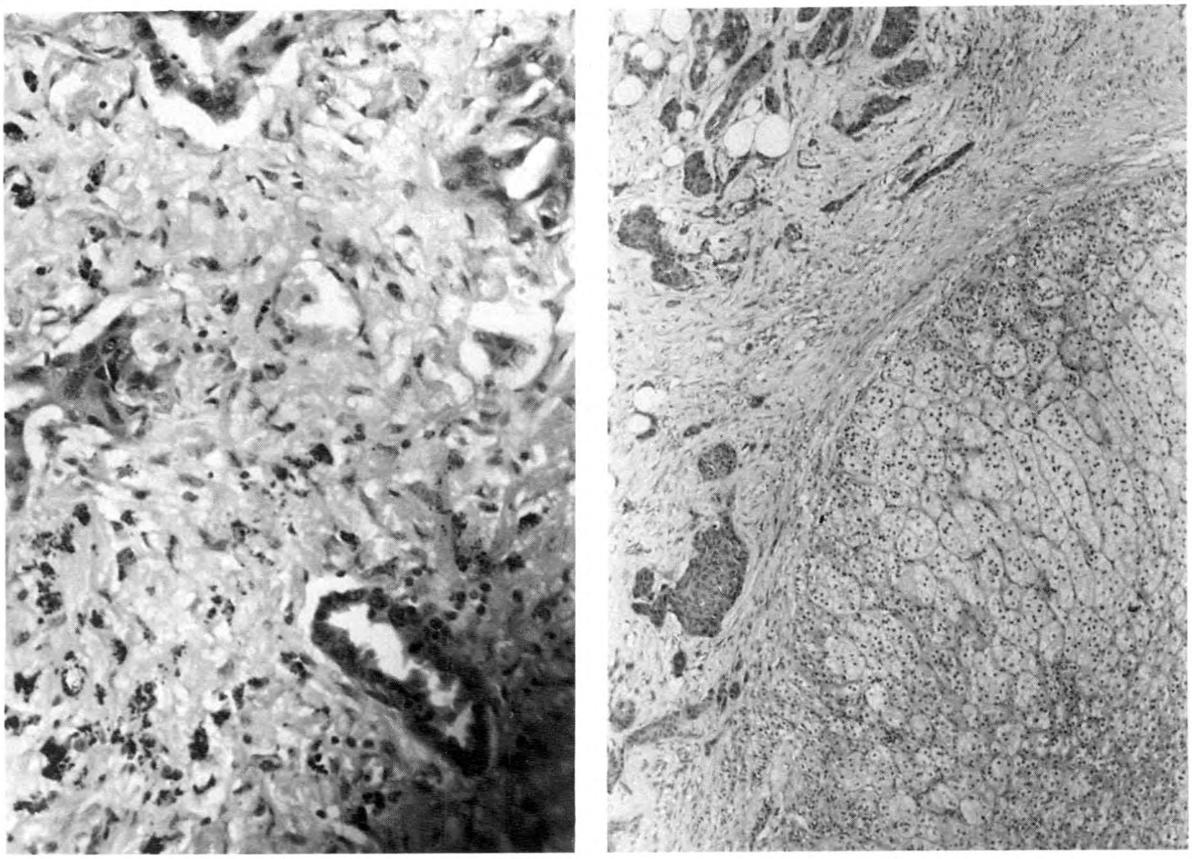

Fig. 4.

Case 2. Histology of the lung tumour (A) and the secondary renal tumour (B). The lung tumour shows the mixed squamous and glandular elements of an adeno-squamous carcinoma. Squamous-cell carcinoma is seen in the pararenal fat and lymphatics, with a similar pattern to the lung tumour. H & E × 170.

lobectomy. On an intravenous urogram the pelvicalyceal system on the left failed to fill adequately, despite a second injection of contrast medium, and the pelviureteric junction and upper ureter appeared displaced laterally (Fig. 5). Renal ultrasound showed a possible renal mass. Renal arteriography showed that the left renal artery was elongated, narrowed and encased. No tumour circulation was seen, nor was there any filling of the renal vein (Fig. 6).

In view of the similarity to the first case, computed tomography (CT) of the renal areas was performed in an effort to define the lesion more clearly. This showed a mass arising from the kidney, invading the pelvis and para-aortic nodes and invading muscle posteriorly (Fig. 7). The left kidney was explored through a loin incision. The findings were a vascular, congested kidney, displaced downwards and laterally by a mass of para-aortic glands, surrounding and invading the renal pelvis. The mass was irresectable, biopsies were taken

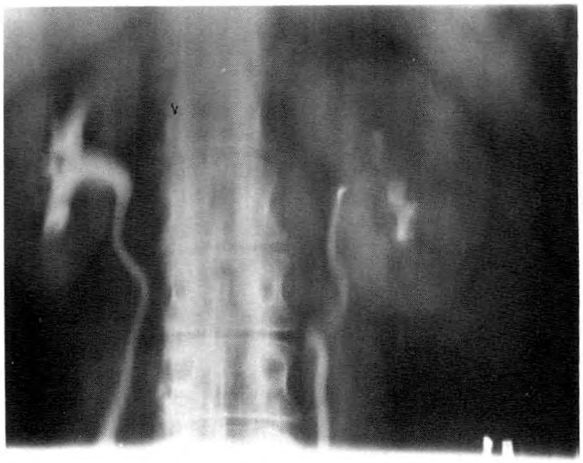

Fig. 5.

Case 2. Intravenous urogram showing poor filling of the left renal pelvis and displacement of the upper ureter.

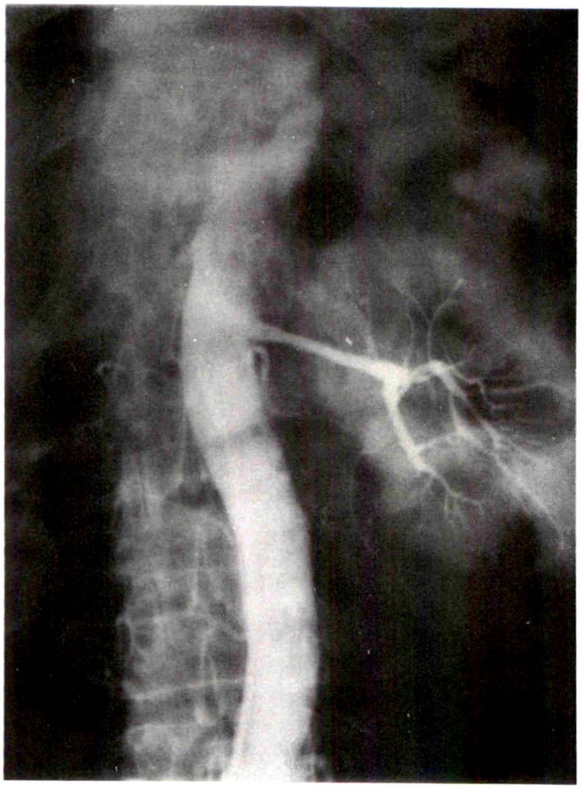

FIG. 6.

Case 2. Selective renal arteriogram showing narrowed and encased renal artery.

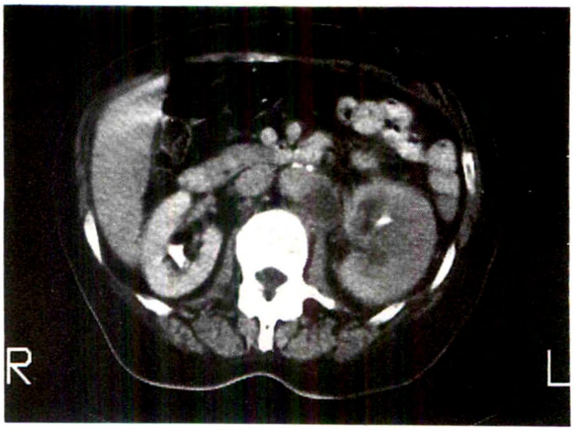

FIG. 7.

Case 2. Computed tomogram showing a left renal mass involving the pelvis, para-aortic nodes and muscle posteriorly (L+40, W 500).

and the wound closed. Histology showed the lesion to be lymphatic metastases from an adeno-squamous carcinoma similar to that excised from the lung (Fig. 4). Post-operatively, the patient was treated with radiotherapy and was still alive, though with progressive disease, 6 months after treatment.

DISCUSSION

The two patients both presented the classical triad of renal pain, renal mass and haematuria. There was no evidence on chest radiography or bone scintiscan of metastatic disease, either from the previously treated lung carcinoma or from the supposed renal carcinoma. The findings on urography, arteriography, ultrasonography and, in one case, CT were thought to suggest primary renal malignancy. An important observation common to both arteriograms was the absence of a venous phase and the appearance of encasement and elongation of the renal artery. In both cases the renal axis was rotated.

It is recognised that renal tumours may give rise to solitary lung metastases some years before the renal tumour becomes clinically obvious. The situation in which metastases from a previously resected carcinoma of the lung present with signs and symptoms suggestive of a renal tumour is less well recognised.

The possibility of secondary neoplasms causing focal renal enlargement is illustrated by Davidson (1985). Deposits of malignant melanoma have been described presenting as an abdominal mass with urinary tract infection (Goldstein et al, 1974). In spite of these reports, the two patients presented here were not diagnosed pre-operatively, suggesting that radiologists and urologists are not sufficiently aware of this problem. Greater awareness that metastases from a primary tumour treated many years previously may mimic renal tumours could avoid needless surgery in such cases. Computed tomography may be more accurate that angiography in staging renal tumours (Probst et al, 1981) but did not differentiate between primary and secondary renal tumour in the patient described here on whom it was performed. It may be that fine-needle aspiration cytology under CT or ultrasound control would allow pre-operative diagnosis and should be performed in patients who have been treated for one malignancy and later present with what appears to be a renal tumour.

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Mammographic changes following radiotherapy

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ABSTRACT

Fifty-seven patients with carcinoma of the breast were assessed with serial mammograms following local excision and radiotherapy. The mammographic appearances due to radiotherapy were categorised and the changes in these with the passage of time have been studied. Residual tumour was identified on the basis of remaining malignant-type microcalcification. Local recurrence was identified on mammography. The most useful signs were the development of a mass lesion and the increase or development of malignant-type microcalcification. Differentiation of radiotherapy changes from recurrence of carcinoma can be made when a reaction that is normally due to radiotherapy occurs to an inappropriate degree, or with inappropriate timing.

Recent advances in the management of breast cancer are characterised by a move towards maximal breast preservation. One increasingly adopted treatment is local surgical excision followed by radiotherapy. This is, however, a problem in that detailed clinical assessment of the irradiated breast is often extremely difficult, particularly in the relatively early post-irradiation period. The use of mammography is, therefore, potentially of great importance in order to detect residual or recurrent tumour. The value of mammography, however, depends on the ability to differentiate appearances induced by radiotherapy from those changes due to neoplastic activity.

For this reason it was decided to categorise the mammographic appearances following radiotherapy, and to study how these change with the passage of time. In addition, evidence which could indicate the presence of residual or recurrent tumour has been identified, together with various miscellaneous findings which may be detected on the mammograms of patients following breast irradiation.

MATERIALS AND METHODS

The study is based on a series of 114 patients with primary breast cancer treated since 1979 by local excision of the tumour, followed by external beam irradiation. Full clinical details of this series are the subject of a separate communication (Morgan et al, 1983). The excision of the tumour was accompanied by axillary and internal mammary lymph node excision for staging purposes. Irradiation was commenced 1–3 weeks after surgical excision and was administered using a 6 MV linear accelerator, giving a dose of 45–50 Gy to the whole breast over a period of 5 weeks. This was followed by a boost of 10–20 Gy to the tumour bed, the total dose to this region being at least 60 Gy.

Mammographic changes due to irradiation

Radiation changes included in the breast are time-dependent and, to study this aspect, all the mammograms of those patients in the series who had had at least three examinations during the period of follow-up were studied in detail. There were 57 patients in this subgroup, with a total of 207 examinations.

The mammographic–histological correlation has not been undertaken as part of this study but is summarised by Paulus and Libshitz (1979).

Features previously demonstrated on histological studies following radiotherapy are: skin thickening (Lever, 1967), trabecular thickening (Paulus and Libshitz, 1979), oedema (Lever, 1967) and calcification (Libshitz et al, 1977).

All the mammograms were studied independently by two observers who specifically identified the presence or absence of the above features, together with the subcutaneous reaction (Roebuck, 1984) and these were categorised according to severity on a five-point scale. The features and the histological changes reported to be associated with them are listed in Table I.

The results of these observations were tabulated and analysed in terms of the time relationship to the radiotherapy (Table II).

Influence of parenchymal pattern

In an attempt to confirm a clinical impression that the radiotherapy changes observed on a mammogram

TABLE I

CHANGES DUE TO IRRADIATION

Mammographic feature	Histopathological change
Diffuse increase in density with ill-defined margins, generalised or segmental	Intracellular plus extracellular oedema
Generalised trabecular thickening	Increased lymphatic drainage and collagen bundle oedema
Skin thickening, local, generalised or periareolar	Skin oedema
Subcutaneous reaction	Lymphatic and small vessel prominence with subjacent oedema or inflammation
Benign-type calcification	Dystrophic calcification

TABLE II

MEAN VALUES FOR EACH FEATURE AS SCORED BY THE TWO OBSERVERS USING THE FIVE-POINT RATING SCALE

	Pre-treatment	Time in months after treatment								
		3	6	9	12	15	18	24	30	36
No of films (total = 207)	26	16	34	14	31	14	26	18	17	11
Oedema										
E J R.	0.39	0.69	1.03	0.22	0.28	0.29	0.08	0.06	0	0
J.B.	0.23	0.75	0.76	0.07	0.29	0	0.04	0.06	0	0
Trabecular thickening										
E.J R	0.19	0.50	0.91	0.29	0.68	0.29	0.35	0.29	0.06	0.09
J B	0.04	0.25	0.56	0.43	0.45	0.29	0.35	0.12	0.12	0
Subcutaneous reaction										
E.J.R	0.35	1.44	1.71	1.07	1.09	0.71	0.27	0.12	0.06	0.36
J.B	0.38	1.06	1.32	1.00	0.71	0.29	0.12	0.06	0.12	0.36
General skin thickening										
E.J.R.	0	1.12	1.21	1.14	0.90	0.93	0.27	0.53	0.06	0.18
J.B.	0.08	0.81	1.18	1.00	0.97	0.79	0.23	0.41	0	0.18
Periareolar skin thickening										
E J R	0.19	1.56	1.79	1.43	1.32	1.50	0.85	0.88	0.65	0.63
J.B	0	0.63	1.24	0.79	0.93	0.86	0.27	0.53	0.23	0.63
Skin thickening										
E J R	0.04	0.56	0.24	0.29	0.19	0.21	0.12	0.18	0.24	0.45
J.B.	0	0.25	0.38	0.43	0.45	0.14	0.15	0.24	0.47	0.45
Scar										
E J R.		0.87	0.83	0.78	1.03	1.22	1.08	1.18	1.24	1.36
J B		0.88	1.03	0.78	0.93	1.22	0.73	0.82	0.82	0.75
Parenchymal deformity										
E.J.R.		1.00	1.09	1.22	1.00	1.64	1.27	1.12	1.47	1.28
J B.		0.75	0.79	1.00	0.83	1.21	0.68	0.53	1.29	1.12

were more severe with a "D"-type parenchyma than a "P", the breast parenchymal pattern in each case was classified according to the Nottingham expansion of the Wolfe classification (Roebuck, 1982).

Evidence of residual tumour

The region of the tumour bed on the first available post-operative mammogram was scrutinised by both observers in every case in the series. A comparison was made with any available pre-operative radiographs in order to detect evidence of residual neoplasm.

Mammographic changes due to tumour recurrence

In order to study the changes associated with recurrent tumour, the mammograms of the six patients in the series with proven recurrent local disease were

TABLE III

SIGNS OF LOCAL RECURRENCE OF TUMOUR

	Patient					
	M D.	J.C.	M.B.	P.P.	H.P.	S.P.
Interval between resection and recurrence (months)	24	33	9	21	15	19
Mammographic Sign						
Trabecular thickening	−	+	−	−	−	−
Segmental oedema	−	+	−	+	−	+
Subcutaneous reaction	−	−	+	+	−	+
Skin thickening	−	−	−	−	−	−
Mass lesion	+	+	+	+	−	+
Calcification (increasing)	+					
(developing)		+	+	−	+	−
Parenchymal deformity	−	−	−	+	−	−
Visible lymph nodes	−	−	−	−	−	−

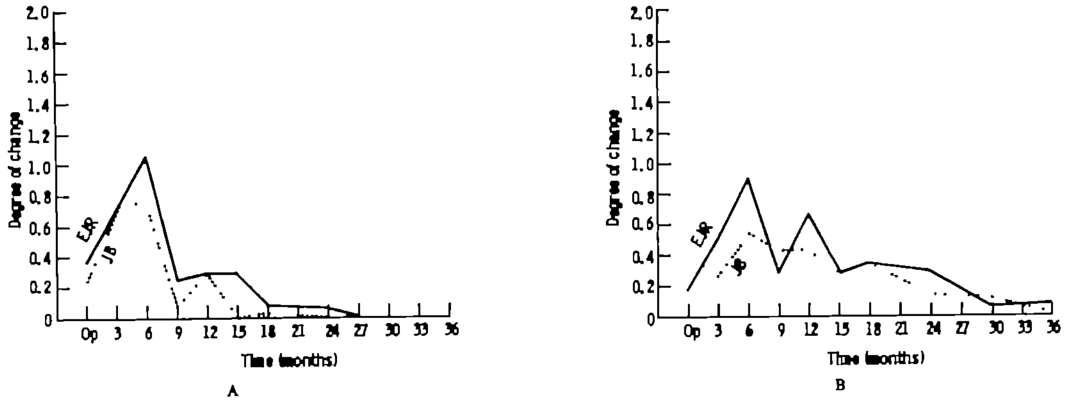


FIG 1.

(A) Generalised oedema. (B) Trabecular thickening by oedema.

studied separately for evidence of the eight features listed in Table III.

Miscellaneous observations

Other mammographic features possibly associated with radiotherapy noted during the scrutiny of the mammograms were recorded.

RESULTS

Changes due to irradiation

The score indicating the degree of severity of each feature as judged by each observer was averaged over the total number of radiographs available at each time interval, the times being related to the operation date.

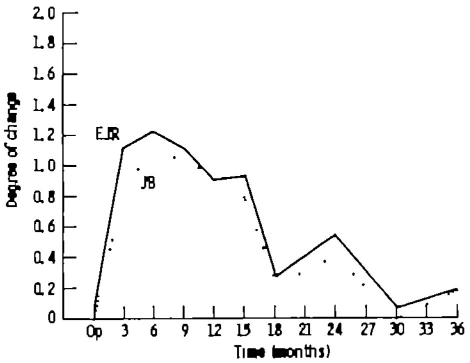


FIG. 2.

Generalised skin thickening.

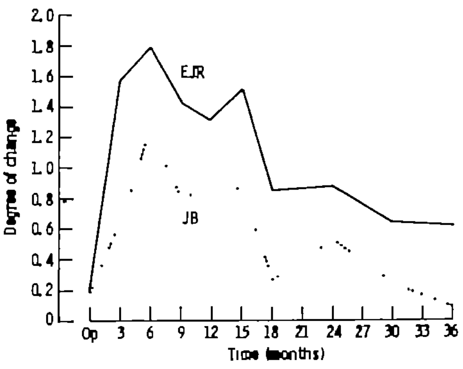


FIG 4

Periareolar skin thickening

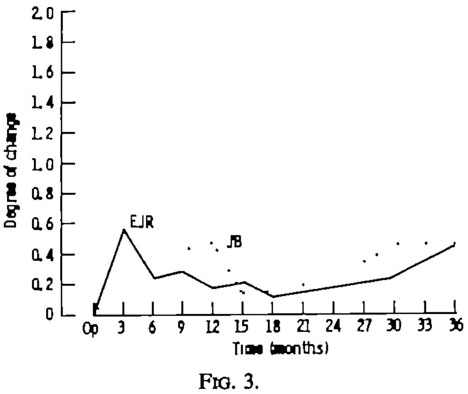


FIG. 3.

Local skin thickening.

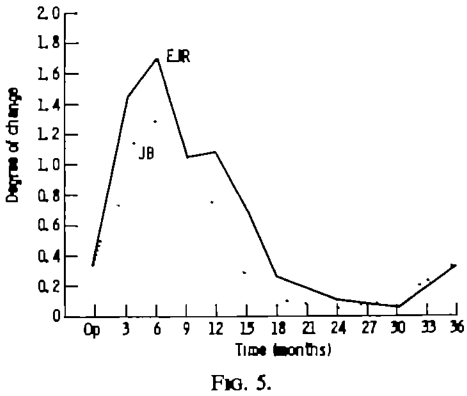


FIG. 5.

Subcutaneous reaction.

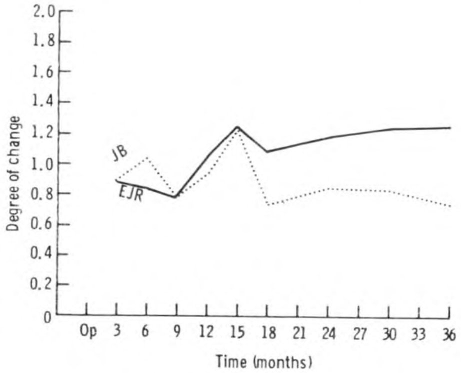


FIG. 6.
Scar formation.

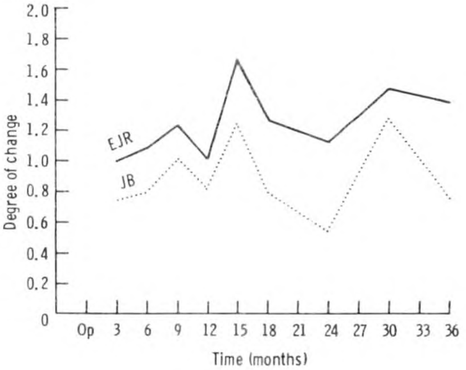
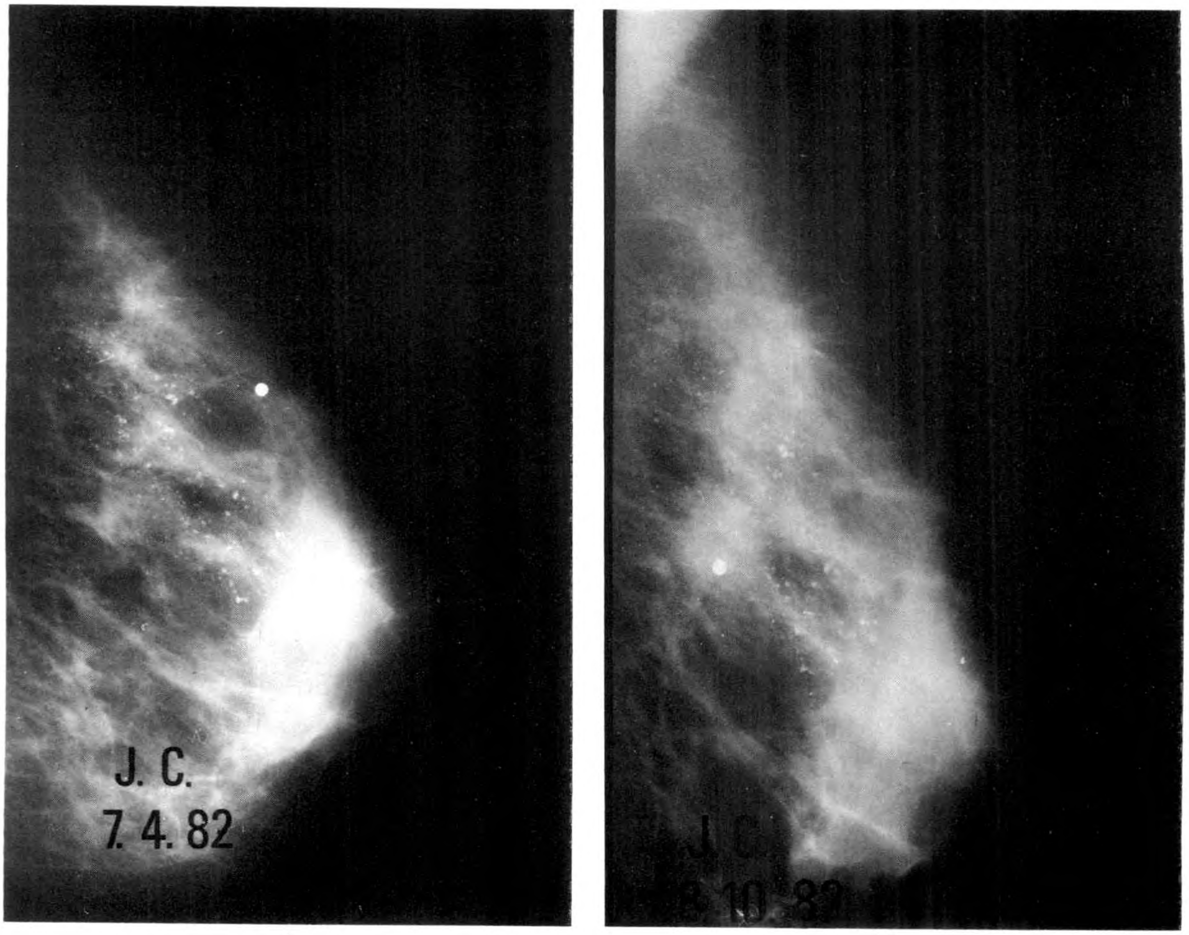


FIG. 7.
Parenchymal deformity.



A

B

FIG. 8.
(A, B) Developing mass indicating recurrence with no change in microcalcification.

The results are summarised in Table II and are expressed graphically for each feature in Figs 1–7.

(a) Oedema. Oedema may occur both intra- and extracellularly and, in addition, a specific entity of oedema of the collagen bundles can be identified (Lever, 1967). Histologically, the oedema is associated with an inflammatory infiltrate. Oedema is demonstrated on film mammography as a generalised or segmental, diffuse, ill-defined density, an appearance which may be contributed to by intra- and extracellular oedema. This feature may not be demonstrated on xeromammograms. The study showed evidence of oedema in all cases, with a progressive increase in the degree of oedema to a maximum which occurs about 6 months after the initiation of radiotherapy. The evidence of oedema was found to resolve in the subsequent 3–6 months (Fig. 1).

It is considered that pure extracellular oedema and collagen bundle oedema are likely to be demonstrated mammographically as trabecular thickening, a feature which was less frequently observed in this series. The changes were found to be maximal at 6 months and to resolve more slowly than intracellular oedema. Some cases of trabecular thickening had not resolved after 30 months, probably due to the development of fibrous tissue in strands alongside the pre-existing collagen bundles.

(b) Skin thickening. This was invariably present to some degree in all cases in the series. The appearance was maximal over the operation site and in the periareolar region. Maximal generalised skin thickening was seen at 6 months, diminishing progressively (Fig. 2). Although most cases of generalised skin thickening had resolved by 18 months, local and periareolar thickening persisted in a few and remained well marked at 36 months. The persistence of thickening localised to the site of excision is considered to be due to surgically induced fibrosis, since in several cases, with no evidence of recurrence, an early increase and subsequent regression were associated with the initial reaction. There was then a subsequent progressive gradual increase in severity (Fig. 3). Surgical interference with the normal lymphatic drainage was considered to be the cause of the very slow decline in periareolar skin thickening (Fig. 4). This persistence was noted to be most marked in cases where the excised lesion had been in the upper outer quadrant or deep to the areola.

(c) Subcutaneous reaction. This mammographic entity has been described fully by Roebuck (1984) and is considered to be the result of increased flow through and, therefore, distension of lymphatic and small blood vessels which, therefore, become visible in the subcutaneous fat. In this series, the appearance was present in all cases in the early post-irradiation period and reached a maximum by 6 months. In virtually all cases it had cleared by 24 months (Fig. 5).

(d) Scar formation and parenchymal deformity. These two features did not show any relationship to the radiation-induced changes (Figs. 6 and 7). It is considered that they result from the surgical intervention and we found no evidence that the development is influenced by radiotherapy.

(e) Calcification. Malignant-type calcifications demonstrated after surgery are taken as evidence of residual tumour, but the persistence of these following radiotherapy does not necessarily indicate tumour activity. An increase in residual malignant calcifications was identified in two cases with proven local recurrence. In seven cases they persisted unchanged, a feature not associated with local recurrence. A decrease in the number of malignant-type calcifications was observed in three cases. A coarsening of the calcific densities, tending to become more similar in appearance to benign-type calcifications, was seen in two cases. These observations were not associated with local recurrence and are taken to indicate cessation of tumour activity. The development of benign-type calcification of the kind associated with secretory disease was occasionally observed to occur in the irradiated breast, but not contralaterally. This confirms the observations of Libshitz et al (1977) and it can, therefore, be assumed that the inappropriate appearance of this type of calcification is in some way stimulated by irradiation.

Influence of parenchymal pattern

The distribution of parenchymal patterns in 57 cases was studied to identify the degree of irradiation

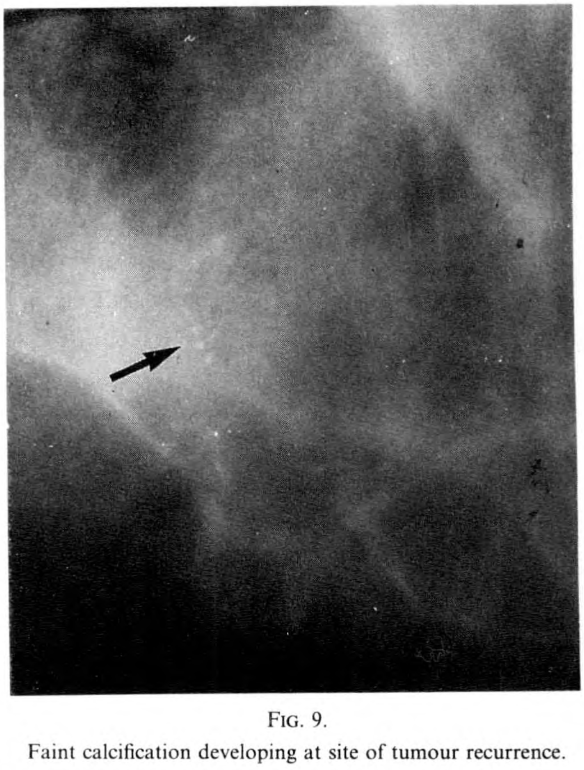


FIG. 9.

Faint calcification developing at site of tumour recurrence.

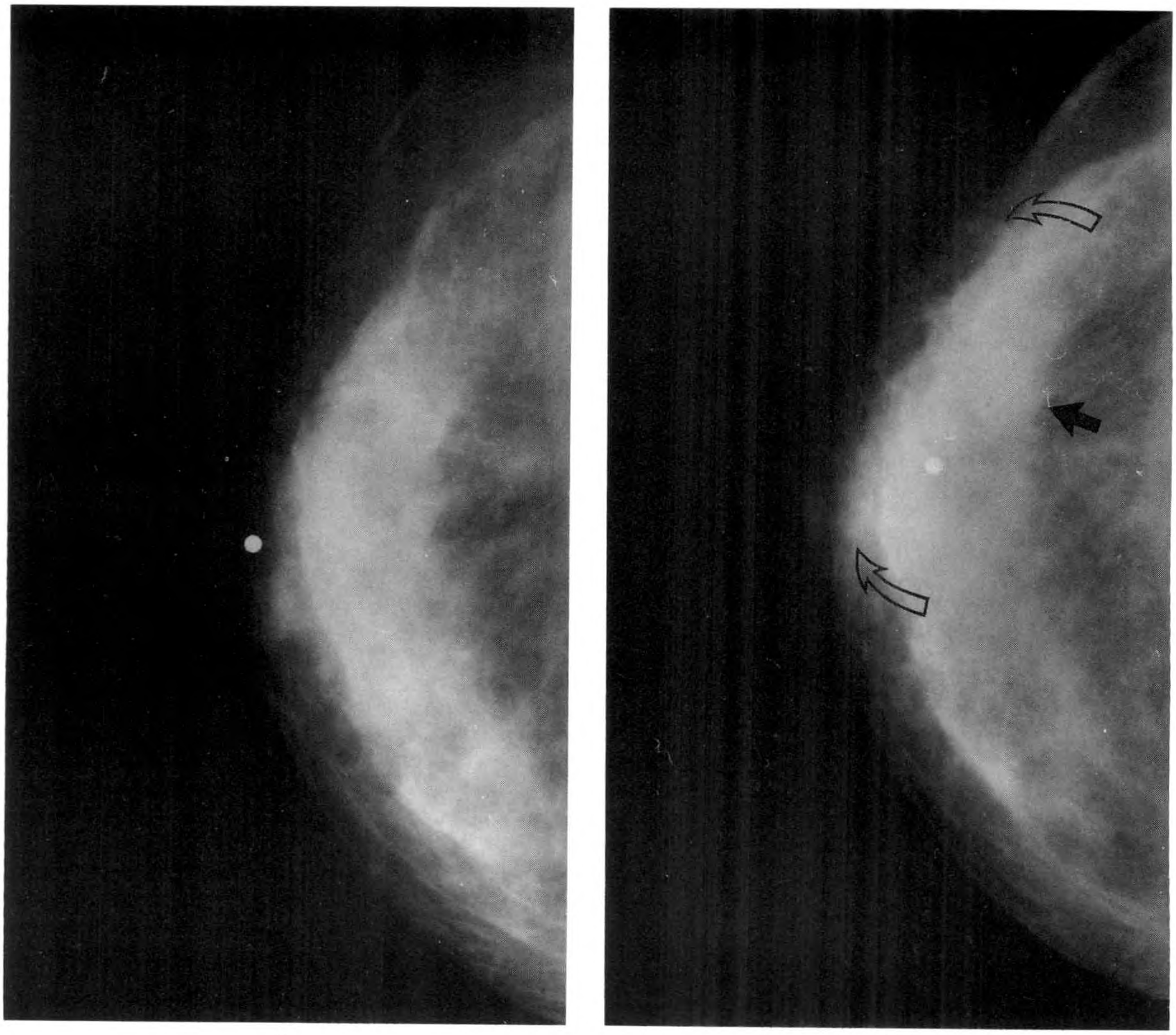


FIG. 10.

(A, B) Mass (solid arrow) and increasing subcutaneous reaction (open arrows) developing over a period of 3 months.

changes. There was no significant difference in the severity of irradiation changes in those individuals with a predominantly "D" parenchyma when compared with those with a "P" parenchymal pattern.

Residual tumour

Evidence of residual tumour was identified in 14 patients in the entire series; in every case it was on the basis of residual malignant-type calcifications.

Tumour recurrence

During the period of follow-up, four patients developed contralateral cancers, emphasising the need for close scrutiny of the opposite breast during follow-up.

Four individuals developed distant metastases and one of these patients also had a local recurrence. Local recurrence was diagnosed in six cases and in all six gave mammographic signs, details of which are summarised in Table III. From this it can be seen that the two most important signs are the development of a mass lesion (Fig. 8) and the increase or development of malignant-type microcalcifications (Fig. 9). Other signs may be masked by the radiotherapy reaction and an early mass lesion may be very difficult to identify amongst the post-operative deformity. An inappropriate increase in the degree of timing of a reaction normally due to radiotherapy should raise the possibility of an underlying recurrence. In our series this sign was identified with respect to the subcutaneous reaction (Fig. 10) and

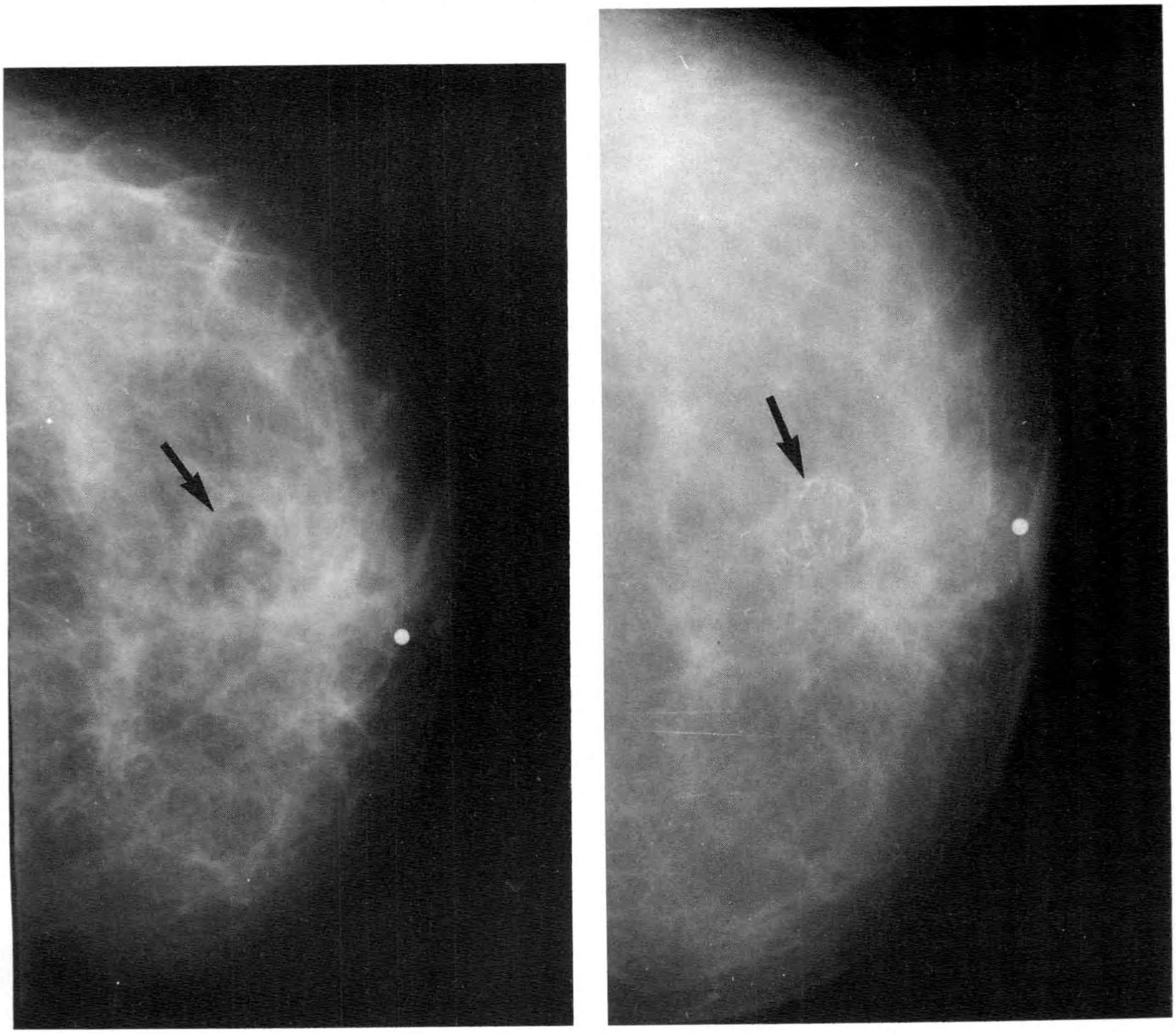


FIG. 11.

(A, B) Calcification developing in the wall of a lipid cyst following radiotherapy (arrows).

the presence of segmental oedema, but not to skin thickening.

MISCELLANEOUS OBSERVATIONS

Pregnancy and lactation

One patient (L.H.) presented with clinical and mammographic evidence of a left-sided primary tumour with axillary metastases and she had an excision of the tumour in April 1981. This was followed by routine irradiation to the left breast and axilla. The patient subsequently became pregnant and in July 1984 delivered a healthy child, which she breast fed from the right breast. Routine follow-up examination, including mammography, was undertaken during the period of lactation.

The mammogram showed a normal lactating right breast, but there was no evidence of lactiferous hypertrophy in the left breast, the appearances on this side being virtually identical to those demonstrated a year previously. It would seem that irradiation renders the alveolar epithelium incapable of the hypertrophy and cellular multiplication necessary for lactation.

Lipid cysts

The development of lipid cysts at the site of surgical excision is a well recognised phenomenon, and in this series was recognised on several occasions. In one case calcification of the wall was observed during the period of follow-up (Fig. 11).

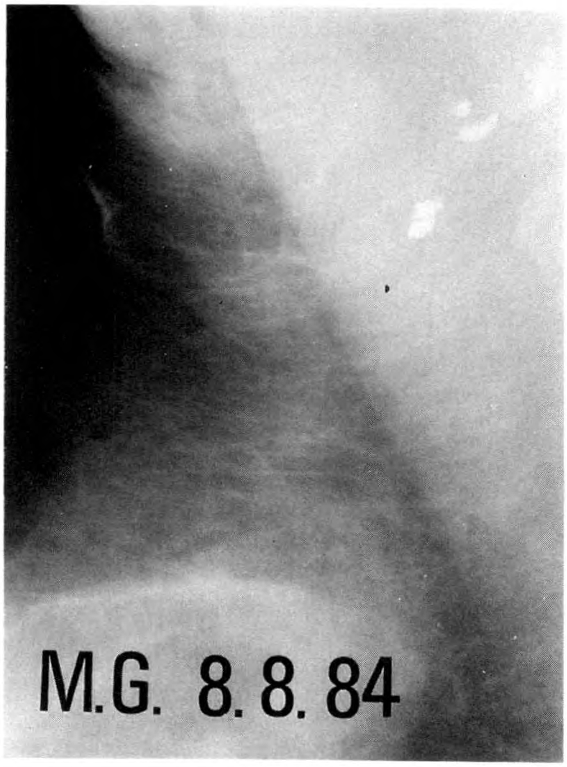


FIG. 12.
Unusual calcification in axilla following radiotherapy.

Dystrophic calcification

Calcification has been reported at the site of the tumour following irradiation (Libshitz et al, 1977). One patient in this series had irradiation to the axilla following histological proof of node involvement and subsequently developed dystrophic calcification in the remaining nodes (Fig. 12).

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Precision of measurement of bone density with a special purpose computed tomography scanner

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ABSTRACT

A new, special purpose, low-dose computed tomography scanner has been developed for the precise measurement of bone density in the distal radius The instrument includes an ^{125}I source and four scintillation detectors which are scanned across a section of the forearm to produce a cross-sectional image. A number of innovative features have been included to improve patient comfort and scanner precision. The reproducibility for trabecular bone measurement was 0.5% for repeated scans in 22 subjects. The long-term precision in a group of normal subjects was better than 5 mg cm^{-3}. The high precision and the separate measurement of trabecular bone make this technique suitable for the longitudinal study of bone density in metabolic bone disease.

A number of methods are currently available for the non-invasive measurement of bone mass in patients with metabolic bone disease. Trabecular bone is metabolically nine times more active than cortical bone because of its greater surface/volume ratio and should show changes in mineralisation faster than cortical bone (Parfitt, 1983). The only non-invasive technique which can measure trabecular bone mass separately from cortical is computed tomography (CT). In order to follow the course of the disease and its response to treatment, the measurement technique should have high precision and there should be no obstacles to inhibit repeated investigations. In osteoporosis bone loss may be increased by about 2% per year; therefore to observe density changes within a reasonable timescale, the reproducibility of the method should be better than 1%.

Using a modified whole-body CT scanner, trabecular bone in the spine can be estimated with a reproducibility of only about 3% (Cann & Genant, 1980; Genant et al, 1982). A whole-body CT scanner has also been used to measure trabecular bone density in the distal radius (Orphanoudakis et al, 1979; Jensen et al, 1980) The mean difference of repeated measurements of a cadaver forearm was less than 2%. However, a slice width of 8 mm was used, and as the mean bone diameter changes typically by 3.5% per mm, difficulties occur in defining the outer edge of the bone and errors in the estimate of bone density result from the partial volume effect. As well as the problem of access to equipment in a conventional radiology department, the use of commercial CT scanners for quantitative measurement of spine and radius requires the simultaneous scanning of a calibration phantom because of the variable output of the X-ray tube.

Special purpose, low-dose CT scanners have been developed, which use a radionuclide source (^{125}I) and measure bone density in the peripheral skeleton (Ruegsegger et al, 1981). Trabecular bone density has been measured in the distal radius with a reported reproducibility of better than 1% in a normal subject. We have designed and built a low cost, self-contained CT scanner which measures trabecular and cortical bone in the radius (Hosie et al, 1985). This is a new design of scanner which uses the same approach as Ruegsegger et al, but incorporates a number of innovative features to increase patient comfort and improve precision. The radiation dose experienced by the patient is low and does not prevent frequent repetition of the measurement. This paper presents the results of an evaluation of the precision of the technique in a group of patients with metabolic bone disease. In a longitudinal clinical trial it is necessary that the measurement technique has long-term reproducibility. Results are presented of bone mass measurements carried out on a group of subjects over a period of 1 year.

MATERIALS AND METHODS

CT scanner

The special purpose CT scanner is of the translational/rotational type and is designed to measure bone mass of the distal radius (Fig. 1). Unlike a commercial scanner which uses an X-ray tube, the radiation source is an 18 GBq (500 mCi) bead of ^{125}I which produces a narrow spectrum of energies around 29 keV. To reduce the scanning time, a multiple-detector (second generation) arrangement is used in which each detector obtains data at a different angle during each translation across the forearm. Four collimated sodium iodide (NaI[Tl]) detectors operating in the count mode are used. This configuration decreases the scanning time by a factor of three compared with a single-detector scanner, while not significantly increasing the size of the scanner. The slice width of each tomographic measurement is 2 mm, and the radiation dose measured by

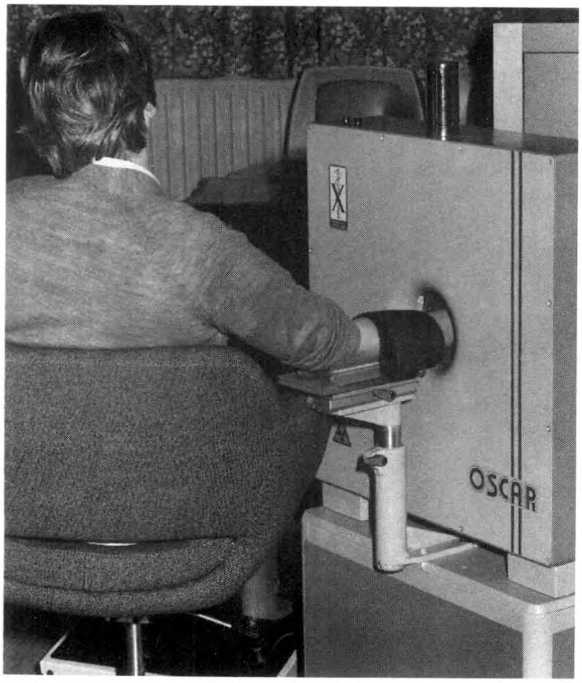

FIG. 1.
Low dose CT scanner for the separate measurement of trabecular and cortical bone in the forearm.

thermoluminescent dosimeter chips was typically 0.4 mSv (40 mRem) for each multislice examination. The half-life of the source is 60 days which requires that it is changed at 3-monthly intervals. The scanner gantry is of a very high precision design. The translation and rotary motion are driven by stepper motors, and to improve patient comfort, axial positioning was achieved, not by moving the patient's arm, but by a third motor driving the whole of the scanner head on linear bearings. The motors are controlled by a microcomputer which is also interfaced to the detector electronics so that the collection of the beam attenuation data can be synchronised with the scanner motion. For each scan, which lasts about 2 min, a total of almost 8000 radiation intensity measurements are made during the 20 translations over a total rotation of 180°. Commercially available microcomputers supplemented by our own design of interface boards were used for motor control, data collection, and imaging. The use of a multiple-processor microcomputer for image reconstruction is one of the principal novel features of the scanner. It is capable of carrying out a number of tasks at the same time, and this enables the image to be reconstructed simultaneously with the data acquisition. Specially developed computer software allows the reconstruction of the cross-sectional image to be completed within 1 min of the end of the scan. This is important, because any movement of the patient during the measurement can be detected, and the scan repeated, if necessary, while the patient is still in position. The operation of the scanner and analysis of the image is controlled by two visual display units. The results of each examination can be output to a printer and stored on flexible disc for future analysis.

Measurement procedure

The length of the patient's ulna, defined as the distance between the palpable tip of the styloid process and the olecranon with the arm in extreme flexion, is measured using a specially designed height gauge. This value and other patient details are entered into the computer by the operator. The patient's arm is secured in the scanner and a scanning radiograph is acquired by moving the scanner head axially by 2 mm between each

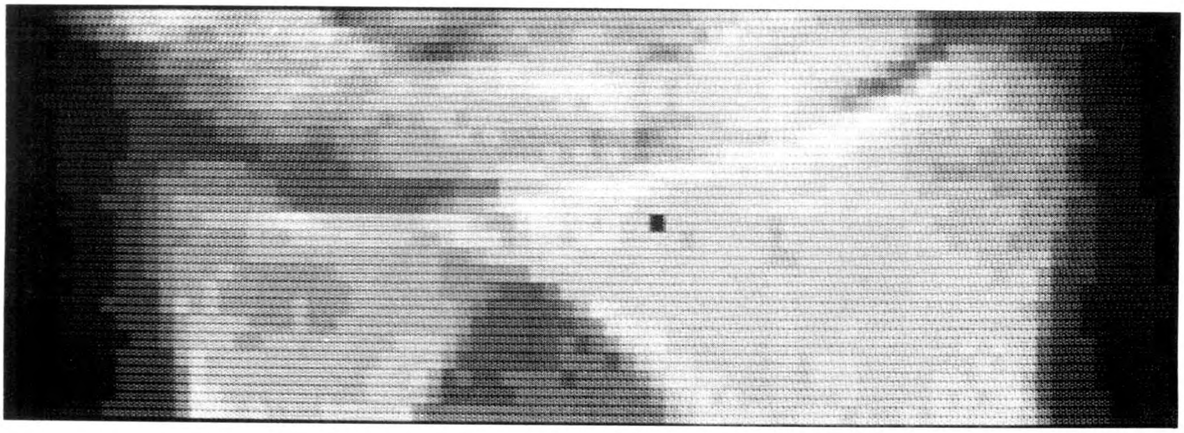

FIG. 2.
Scanning radiograph used to position the scanner accurately. The distal end of the ulna (left) can be clearly defined. The distal end of the radius is less well defined (Hosie et al, 1985).

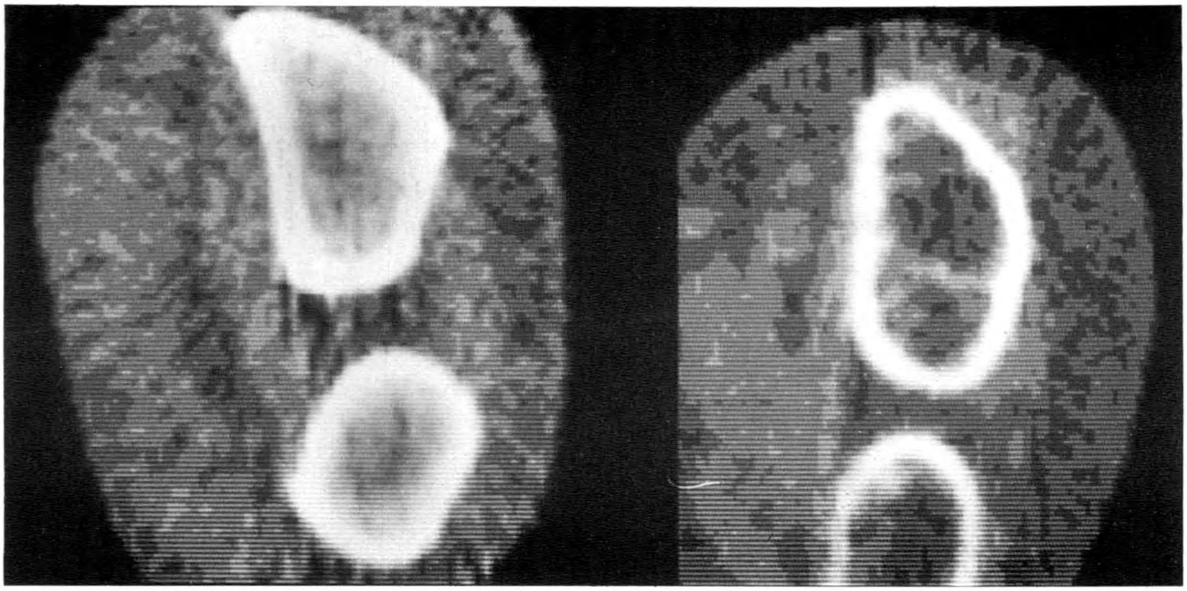

Fig. 3.

Reconstructed cross-sectional images of the distal forearm. The tomograph of a normal subject (left) is compared to that for a severely osteoporotic subject.

of 24 translation measurements. This image is displayed on the colour monitor and the distal end of the ulna defined (Fig. 2). The end of the ulna is used as a marker to identify the measurement site on the radius because it can be easily and accurately identified. The computer positions the scanner at a site at 3% of the ulnar length. Three adjacent slice measurements, each 2 mm wide, are acquired with a fourth measurement made at 25% of the ulnar length. There are significant quantities of trabecular bone at the former sites and the bone content of the latter site is almost entirely cortical bone (Schlenker & Von Seggen, 1976). Figure 3 shows images for two subjects.

The analysis of the images first involves separating the bone from the surrounding soft tissue. This is done using a surface detection algorithm (Hosie et al, 1985). The picture elements (pixels) represent linear attenuation coefficients (CT values) from which it is possible to derive bone density (Hangartner & Overton, 1982). The mean CT value for the entire bone cross-section is evaluated and the mean bone density derived. The total bone mass in the cross-section can also be calculated. At the distal sites the trabecular bone is isolated by stripping off rings of pixels from the bone image until only a 50% core area remains. The cross-sectional area of the radius changes rapidly at the distal measurement site and can be accurately measured from the tomographic images. Thus the area can be used, with linear interpolation between the slices, to identify the same bone sample for all repeat examinations of a patient. This repositioning accuracy is essential, as bone density changes by about 3% per mm change in axial position at the distal measurement site.

Subjects studied

To assess the reproducibility of the scanner over a range of bone density values, a group of five normal subjects (three female, two male) and 17 patients (15 female, two male—mean age 63 years) were scanned on two separate occasions. The patients were a sequential group of subjects who attended the Bone Metabolism Research Unit. Thirteen of the patients were diagnosed as osteoporotic, and four of these had primary hyperparathyroidism. Two of the patients had hypoparathyroidism and two were diagnosed as suffering from thyrotoxicosis and Paget's disease, respectively. Duplicate measurements of the distal radius were made on average 30 days apart (range 5–56 days).

In a longitudinal clinical trial it is necessary that the measurement technique is reproducible over the period of the trial. To assess the long-term precision of the scanner, four normal subjects (two female, age 27 and 41 years, and two male, age 30 and 56 years) were scanned at approximately monthly intervals over a 1-year period.

RESULTS

Precision is normally defined as the standard deviation of a series of measurements. When small samples are made that come from normal populations of the same standard deviation, but different mean values, it is possible to average the estimates of the

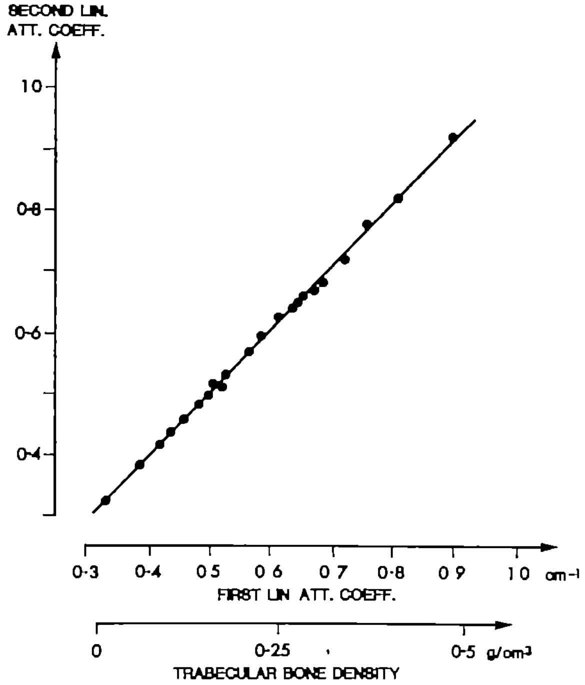

Fig. 4.

Repeated measurements of trabecular bone density in 22 subjects. The extremely high reproducibility of the procedure was 0.5%.

standard deviation to obtain a reliable estimate for the whole set of data (Wilson, 1952). The formula for estimating the standard deviation (σ) is given by:

$$\sigma^2 = \frac{1}{N-k}\cdot\sum_{j=1}^{k}\sum_{i=1}^{n_j}(X_{ij}-\bar{X}_j)^2 \qquad (1)$$

where: X_{ij} is the ith observation of the jth sample
$\bar{X}_j$ is the mean of the jth sample
n_j is the number of members of the jth sample
N is the total number of observations
k is the number of samples

For duplicate measurements (1) reduces to:

$$\sigma^2 = \frac{1}{N}\cdot\sum_{j=1}^{k}(X_{1j}-X_{2j})^2 \qquad (2)$$

The coefficient of variation (CV) is given by:

$$CV = \frac{100\,\sigma}{m} \qquad (3)$$

where: m is the mean value of the set of measurements.

In order that the results can be compared with other CT scanners, the precision of the bone parameters can be expressed in terms of physical units (g cm^{-3}, g cm^{-1}).

The results for the duplicate measurements of trabecular bone in 22 subjects are shown in Fig. 4. The coefficient of variation for the trabecular bone CT value was 0.50% and, when expressed as a physical density, the precision was 2.4 mg cm^{-3}. The reproducibility for all the measured parameters is given in Table I.

The standard deviation for a series of measurements was calculated according to the formula:

$$\sigma^2 = \frac{\sum_i (X_i-\bar{X})^2}{n-1} \qquad (4)$$

where: X_i is the ith observation
$\bar{X}$ is the mean of the sample
n is the number of observations

The long-term reproducibility for trabecular bone measurement is shown in Fig. 5. The mean coefficient of variation for the subjects was 0.73%, corresponding to a precision of 4.8 mg cm^{-3} when expressed as a physical density. Table II details the results for the other measured parameters. The mean trabecular bone CT values for the periods January to March and July to September for the four subjects were found to be identical (0.741 cm^{-1}). An aluminium and perspex phantom, representative of the distal forearm, was scanned daily over the same period. The attenuation CT value was calculated in the same way as for the patient scans. The weekly average is plotted in Fig. 5. The coefficient of variation was 0.37% for 196 separate measurements.

Discussion

A special purpose CT scanner has been developed for the measurement of bone density in the peripheral skeleton. The scanner is self-contained and bone density results can be obtained immediately after the 20 min investigation. Our previously reported results have

TABLE I

Short-term reproducibility

Parameter	Mean value	Average standard deviation	Coefficient of variation	Precision
Trabecular bone	0.584 cm^{-1}	0.0029 cm^{-1}	0.50%	2.4 mg cm^{-3}
Total bone at distal site	0.853 cm^{-1}	0.0084 cm^{-1}	0.99%	7.0 mg cm^{-3}
Cortical bone	1.679 cm^{-1}	0.0222 cm^{-1}	1 32%	18 mg cm^{-3}
Cortical mass per unit length	1.248 g cm^{-1}	0.0164 g cm^{-1}	1 31%	16 mg cm^{-1}

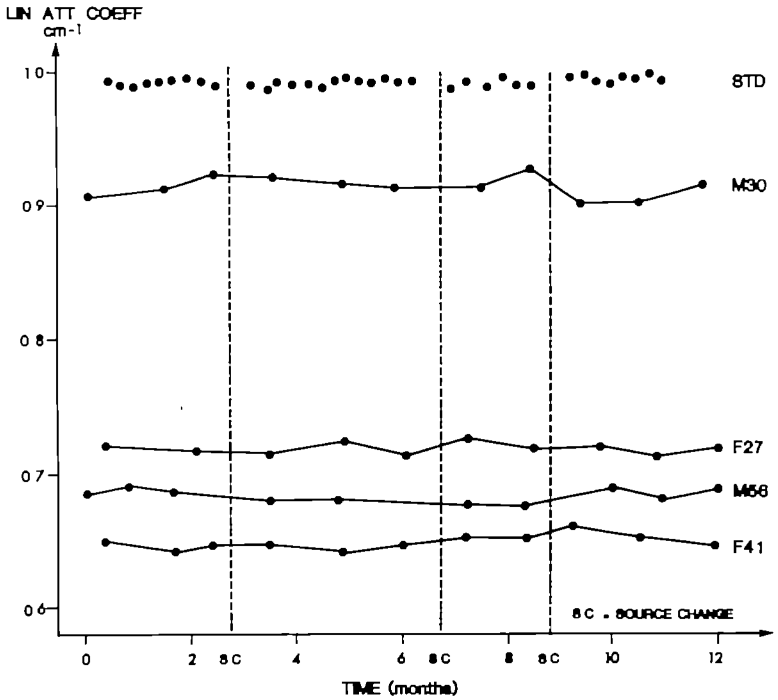

Fig 5.

Reproducibility of bone measurements for four subjects (F41, M56, F27 and M30) and for an aluminium and perspex standard (STD) over a period of 12 months. The mean coefficient of variation for the subjects was 0.73%.

shown a short-term reproducibility of 0.04% in a phantom and 0.3% for trabecular bone in a normal subject (Hosie et al, 1985). Other groups report similar precision for specialised CT bone density measurement in normal subjects (Ruegsegger et al, 1981; Hangartner & Overton, 1982), but no data are available on the reproducibility of the method in patients with metabolic bone disease. We have shown that, with our new design of scanner, trabecular bone can be measured with a reproducibility of 0.5% in patients and normal subjects. The long-term precision of the scanner over a 1-year period is also better than 1%. The 3-monthly source change is a straightforward procedure and no shift in measured density value was found for the four sources used during the scanner evaluation. Using dual photon absorptiometry, Krolner reported a 2% increase in the bone mineral content of the lumbar spine in the period July to September compared with January to March (Krolner, 1983). We did not find any seasonal variation in trabecular bone mass of the radius in the group of normal subjects that we studied.

The extremely high reproducibility of the special purpose CT scanner for the measurement of purely trabecular bone makes it possible to monitor changes in individual subjects with and without therapy. With a reproducibility of about 3%, which is the case for CT and dual photon absorptiometry of the spine, it may take several years of study before significant changes could be measured. The distal radius is not only a convenient location for measuring trabecular and cortical bone but is a common site of fracture in osteoporotic women. Indeed, one third of all fractures in women occur at this site (Knowelden et al, 1964). It may seem that the spine is the preferential site for densitometric measurements because of the chronic backache which results from vertebral crush fracture. Furthermore, measurements of the radius using single photon absorptiometry have been only moderately correlated with the spine ($r = 0.6$) (Wilson, 1977). However, this was a comparison of mainly cortical bone in the radius with predominantly trabecular bone in the spine. A more recent study has reported that trabecular bone at the two sites is highly correlated ($r = 0.926$) (Ruegsegger et al, 1981). Problems can arise in measurement of the spine resulting from crush fractures and wedging which will cause an anomalous increase in trabecular bone density and difficulty in distinguishing individual vertebrae.

TABLE II

Long-term reproducibility for four subjects

Parameter	Mean coefficient of variation	Mean precision
Trabecular bone	0.73%	4.5 mg cm^{-3}
Total bone at distal site	0.79%	6.3 mg cm^{-3}
Cortical bone	1.57%	27 mg cm^{-3}
Cortical mass per unit length	1.41%	25 mg cm^{-1}

When expressing the bone parameters as physical densities, a fixed fat content was assumed. Variation in the relative proportions of red marrow and the fatty yellow marrow will reduce the accuracy of the measurement. This problem also occurs in the measurement of the spine using CT and dual photon absorptiometry. Hangartner and Overton (1982) have estimated an error of 0.4% in the ^{125}I CT measurement of trabecular bone volume (TBV) when the relative proportion of yellow marrow increased from 30% to 60% and the TBV was 25%. This corresponds to an error of 8 mg cm^{-3} in the estimate of trabecular bone density. At the higher average photon energy (70 keV) used in X-ray CT of the spine, a similar change in marrow content would result in a large error of 15 mg cm^{-3} in the estimate of trabecular bone density. During a longitudinal clinical trial the change in marrow composition should be significantly less and the precision would be only minimally affected. Dual energy CT could potentially eliminate the problem of marrow variability. However, the precision of dual energy CT is many times worse than single energy CT, and the technique has not yet been applied in routine clinical practice.

ACKNOWLEDGMENTS

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The potential accuracy of dual-energy computed tomography for the determination of hepatic iron

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ABSTRACT

Physical experiments are described which simulated the main practical and technical problems encountered in estimating iron concentrations in liver by dual-energy computed tomography In aqueous solutions located in an oval water phantom, the presence of Fe at concentrations of 1 and 2 mg/ml was detected and estimated with good accuracy and reproducibility The main physical problem was that water showed a non-zero dual-energy difference reading whose magnitude varied with location, but this potential error was largely eliminated by measuring the location-specific water values using a technique readily adapted to patient studies. Experiments with pieces of bovine tissue in the same system suggested that the dual-energy response shown by liver tissue may include an Fe-independent contribution, reflecting its organic composition (including fat content): if attributed to Fe, this would correspond to an error $< \pm 1$ mg/g wet weight in the evaluation

The experiments described were done to give a provisional estimate of the accuracy of dual-energy computed tomography (CT) in order to support its projected use for non-invasive assessment of hepatic iron concentrations in children with β-thalassaemia. Correlation with chemical data from biopsy specimens is perhaps the ultimate test of accuracy but, possibly because opportunities for obtaining biopsy data are limited, no detailed study of this kind has been reported since that of Chapman et al (1980) who used the EMI CT/5005 scanner. By contrast, the present study was done using each of two current CT models and a test system which simulated the main practical and technical conditions of a patient investigation. This allowed identification of the various errors and the development of practical methods for reducing them.

The scanners used were a GE 9800 at the Royal Children's Hospital, Melbourne, and a Siemens DR3 at the Peter MacCallum Hospital. Both were standard models in routine working condition Dual-energy operating conditions were 80 kV, 240 mAs and 140 kV, 80 mAs with the GE 9800 scanner and 96 kV, 230 mAs and 125 kV, 120 mAs with the DR3 scanner. Slice widths were 5 mm (4 mm for the DR3) and images were reconstructed using field-of-view (FOV) diameters of 34.5 cm or 31 cm (medium body file with the GE 9800, zoom factors 1.5 or 1.7 with the DR3). The experiments involved scanning two water-filled phantoms which had provision for internal mounting of plastic flasks containing aqueous solutions of ferric sorbitol citrate (Jectofer, Astra Chemicals, Sydney) having known Fe concentrations. These (locally made) phantoms, oval in cross-section (32 cm × 22 cm and 28 cm × 20 cm), were designed to resemble abdominal cross-sections for calibrating dual-energy patient studies. In these experiments, the patient was represented by a "target" section of the larger phantom, which contained two unknown solutions whose Fe concentrations were to be estimated and compared with the known values (1 mg and 2 mg Fe/ml). Calibrations, to establish water values and the relation between CT and Fe parameters, were done using another section of this phantom, or the smaller phantom.

Table I shows data from an experiment using the GE 9800 scanner which consisted of four pairs of scans of the target section (80 kV followed by 140 kV, performed four times), and three pairs of scans of the smaller calibration phantom. Figure 1A shows an 80 kV image of the target section, with regions of interest set to record average Hounsfield numbers ($N_{U,L}$) for the two unknowns at locations designated 1 and 2. The same regions were transferred directly to the 140 kV image to record the $N_{U,H}$ values. For each unknown, the concentration (mg Fe/ml) is given by.

$$c = \{(N_{U,L} - N_{W,L}) - (N_{U,H} - N_{W,H})\}/k$$

where $N_{W,L}$ and $N_{W,H}$ are water values, defining the true zeros of the low-energy and high-energy scales and, by previous measurements (Sephton, 1985), the conversion factor k is 2.2 HU per mg Fe/ml. In the work cited, the GE 9800 scanner showed systematic variations in ($N_{W,L} - N_{W,H}$) across the oval section, hence the present experiments included measurements of water values corresponding to the specific regions of interest. These data were obtained by scanning an adjacent water section in the same phantom but, to simulate a patient study where none of the available calibration phantoms would precisely match the patient cross-section, alternative water corrections ($N'_{W,L}$, $N'_{W,H}$) were also obtained from scans of the smaller phantom. To allow direct transfer of regions from the target section (reconstruction FOV 34.5 cm), those images were reconstructed using FOV diameter 31 cm (as in Fig. 1B, showing Region 2 transferred from Fig. 1A). Table I presents calculations for each unknown, using $N_{U,L}$ and $N_{U,H}$ data from one of the four pairs of target section images corrected by water

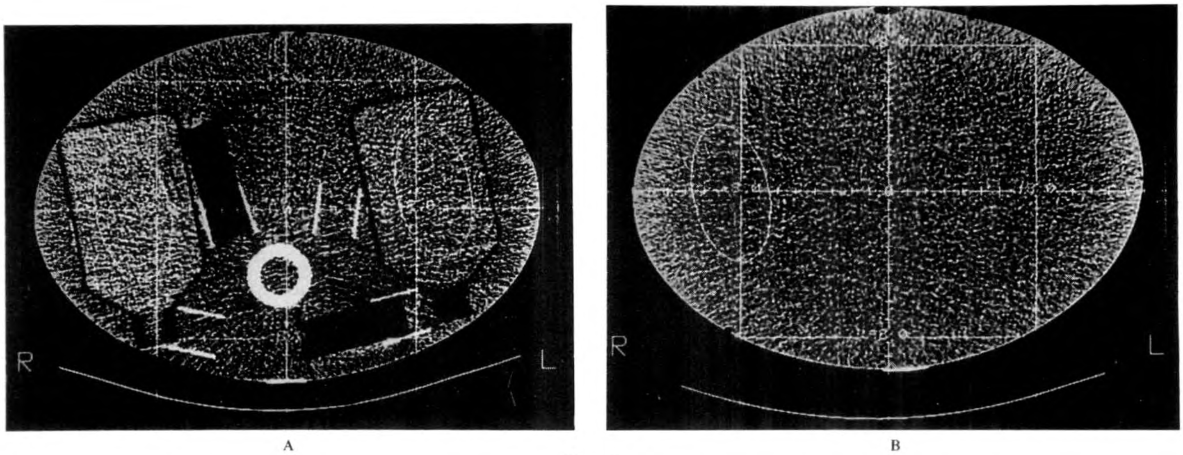

FIG. 1.

(A) Target section, with oval regions at Locations 1 and 2. (B) Calibration (water) section, with Region 2 transferred from (A).

values $N'_{W,L}$, $N'_{W,H}$ averaged from the three pairs of calibration scans. Within the experiment, k was monitored by scans at a different section of the water phantom, which included a standard solution (10 mg Fe/ml, density 1.035 g/ml) placed at a relatively central location 3 (image not shown). From the four sets of target section data, estimated Fe concentrations for the 2 mg/ml and 1 mg/ml solutions were 1.85 ($\pm$0.15) (SD) mg/ml and 0.9 ($\pm$0.15) mg/ml, respectively.

Using a GE 9800 scanner there were five such experiments performed over a period of 12 weeks. The mean values ranged 1.6–1.9 mg Fe/ml and 0.7–1.1 mg Fe/ml, the corresponding means being 1.75 ($\pm$0.15) mg/ml and 0.9 ($\pm$0.15) mg/ml. In the typical experiment, estimates were increased by approximately 0.2 mg/ml if the theoretically better water corrections obtained using the identical phantom were applied. As shown in Fig. 1, the target section contained additional features—a 6 mm wide ring of Teflon ($\sim$900 HU) and two air cavities ($-$970 HU at both energies)—which were not present in the water sections. In two experiments the target section scans were repeated after removal of these additional "structures", but the Fe estimates were only marginally changed. The general experience indicated that the presence in the patient section of structures such as spine and bowel gas would not seriously perturb the dual-energy data at liver locations.

Two detailed experiments were performed using the Siemens DR3 scanner and the estimates obtained were 2.1 ($\pm$0.3) mg Fe/ml and 1.2 ($\pm$0.5) mg Fe/ml, and 2.4 ($\pm$0.6) mg Fe/ml and 1.1 ($\pm$0.5) mg Fe/ml. As reported previously, k for the DR3 scanner was 1.2 HU per mg/ml. However, variations in $(N_{W,L} - N_{W,H})$ across the field were also relatively small and, in fact, with the data from the first experiment recalculated using water corrections from the central location only, estimated values were 2.6 mg Fe/ml and 1.6 mg Fe/ml.

In evaluations of liver tissue as opposed to aqueous solutions, the dual-energy difference might contain an Fe-independent component if the tissue itself, by virtue of its organic composition, had an effective atomic

TABLE I

ESTIMATION OF IRON, USING THE GE 9800 SCANNER

	Fe solutions		Hounsfield numbers at		Corrected	Estimated
	Location	mg Fe/ml	80 kV (N_{80})	140 kV (N_{140})	($N_{80}-N_{140}$)	(mg Fe/ml)
Target section (32 cm × 22 cm)	1	1	2.3	4.7	2* HU	0.9
	2	2	11.2	10.9	4.3 HU	1.95
Water section (28 cm × 20 cm)	1	0	$-$4.8	$-$0.4		
	2	0	$-$4.4	$-$0.4		
	3	0	$-$1.8	$-$0.8		
	3†	10	83.2	62.2	22 HU	

* Corrected as $(2.3+4.8)-(4.7+0.4) = 2$ HU.

† Section intersecting iron standard (10 mg Fe/ml), to confirm $k = 2.2$ HU per mg Fe/ml.

number different from water. If significant, this component would represent a "biochemical" uncertainty which should be resolved. For provisional data on the question, a slab of calf liver tissue fitted into a plastic container was placed in the larger phantom and a dual-energy evaluation was made using the GE 9800 scanner. Average (corrected) CT numbers were 52.5 HU and 51.8 HU at 80 kV and 140 kV, respectively, giving a difference value of 0.7 (±0.35) HU. In a subsequent experiment, ox liver showed 72.5 HU and 70.6 HU (difference 1.9 ± 0.3 HU) and a slab of fat showed −76 HU and −58 HU (difference −18 HU). If normal bovine liver is comparable with human liver (*i.e.* <0.25 mg Fe/g wet weight) the dual-energy difference due to Fe should be <0.5 HU using the GE 9800 scanner. These limited experimental findings suggest that the biochemical component might introduce an error approaching +1 mg Fe/g wet weight in normal livers, reducing with increasing fat content and even becoming negative in extreme cases. Since the absolute CT number of the liver would also depend on fat content, the required corrections might be worked out on the basis of the recorded absolute value

These observations on the potential accuracy of the method may now be related to published data on chemically determined hepatic Fe concentrations in patients with β-thalassaemia. Barry et al (1974) reported on 18 cases with Fe concentrations ranging from 1% to 5% dry weight, *i.e.* 10–50 mg Fe/g dry weight, which corresponds to ~3–15 mg/g wet weight. In the present experiments the dual-energy method detected Fe in solution down to 1 mg/ml (*i.e.* ~1 mg/g wet weight) accurately and reproducibly to within about 0.2 mg/ml. The data from patient studies should be of comparable accuracy if corrected using location-specific water values as described. The clinical practicability of the methods depends only on choosing the most appropriate of a range of (relatively uncomplicated) oval phantoms. In contrast, the marginally more convenient calibration methods involving standards located peripherally in the patient section would not give accurate water values. The biochemical uncertainty might, in fact, be more significant than physical inaccuracies, but would be unlikely to exceed ±1 mg/ml. It is suggested that simulation experiments such as those described provide specific information which is not practically obtainable from direct clinical studies and which should give reliable guidance on the rational use of dual-energy CT for non-invasive monitoring of hepatic iron.

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Book reviews

Radiotherapy Treatment Planning 2nd edit Medical Physics Handbooks, 14 By R. F. Mould, pp. xv+256, 1985 (Adam Hilger, Bristol), £19.50/$29 00.
ISBN 0–85274–788–8

This second edition is an enlarged version of Volume 7 in the Medical Physics Handbook series. Much of the original text has been retained unaltered while several chapters have been expanded to take in new developments and to update the older techniques. The text is profusely illustrated—so very necessary in a book of this type—and the larger format of the book has enabled the text/diagram ratio on some pages to be improved. The reader, however, is still left turning on several pages to find the figure referred to in the text. This could have been largely avoided by omitting the repetitious photographs of equipment and reducing in size some of the very adequate diagrams

The early chapters introduce the reader to therapy beam equipment of all energies and the parameters which characterise their beams. The lengthy Chapter 5 deals with the isodose patterns from some standard and some not so standard field arrays, patient contouring and beam-direction devices The new material at the end of this chapter outlines mantle field and total body irradiation techniques. The calculation of dose in the difficult and sometimes obscure situations arising in clinical radiotherapy is dealt with in Chapter 8. These outlines are very adequate in most cases and refer the reader to the original publications for further reading as necessary. The inclusion of a section on the empirical formulae for dose fractionation, such as TDF, NSD and CRE, shows the extent to which the author has gone to cover the calculations which may land on the physicist's desk. Brachytherapy is also included, but only insofar as it affects the external-beam treatment plan. There is some useful guidance on what to expect from and to look for in commercially available computer planning packages along with some discussion on quality assurance of the system in use. The systems are not all equally good, or equally bad, when it comes to the presentation of the results.

This handbook is a valuable asset to anyone interested in treatment planning either as a student or as a practising physicist or technician. While the references quoted enable the reader to go deeper in the subject, the text is not as deep when compared with other handbooks in this series. It will be widely used as a teaching aid.

C. K Bomford

Malignant Tumours of the Oral Cavity. By J. M. Henk and J D. Langdon, pp x+235, 1985 (Edward Arnold, London), £29.95.
ISBN 0–7131–4453–X

This monograph is one of the "Management of Malignant Disease" series It is a short, compact book which discusses fully all aspects of tumours of the oral cavity, including aetiology and the immunological and virological aspects of oral cancer. The various controversies in the management of oral cancer are well presented and, while every reader might not agree with the conclusions reached, the facts are all well marshalled. The causes of failure of treatment and prognostic factors in oral cancer are presented There is a comprehensive discussion of the various methods of radiotherapy together with a relatively brief discussion of surgical alternatives Of recent monographs on this subject, this is by far the best and will be found useful to all clinicians concerned in the management of oral cancer. There are profuse references and the presentation makes it a very readable book.

R C S. Pointon

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Correlation of human NMR T_1 values measured *in vivo* and brain water content

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ABSTRACT

A relationship has been demonstrated between nuclear magnetic resonance (NMR) longitudinal relaxation times (T_1 values) obtained *in vivo* in both normal and oedematous (peritumoral) brain tissue, and measurements of brain water obtained by gravimetric analysis of operative samples. Significant correlations were found in seven patients in both cortex ($r = 0.97$, $P < 0.001$) and white matter ($r = 0.92$, $P < 0.001$). These findings suggest that NMR may prove a useful technique for monitoring brain oedema.

Nuclear magnetic resonance (NMR) T_1 values in body tissue are considered to be related to total water content and to the ratio between "free" and "bound" water (Go & Edzes, 1975; Mathur-De Vré, 1984). Longitudinal relaxation time (T_1) lengthens in oedematous tissue and in a variety of pathological conditions including malignancy. Previous authors (Go & Edzes, 1975; Naruse et al, 1982) have shown a linear correlation between T_1 of experimentally induced cerebral oedema, measured by *in vitro* NMR spectrometry, and brain water, calculated from the weight of wet and dry tissues. The present study was performed in order to examine the relationship between T_1 values, obtained from clinical NMR images of patients about to undergo surgery for cerebral tumour, and brain water measurements obtained by gravimetric analysis of the excised specimens, and also to establish whether T_1 images can be used to predict the degree of cerebral oedema.

METHOD

Patients

All seven patients examined had histologically verified solitary tumours within the brain. Six were gliomas and the seventh a metastasis from an adenocarcinoma of lung. All patients were receiving 4 mg dexamethasone four times a day at the time of imaging and surgery. Four of the patients received 200–500 ml 20% mannitol at the time of dural opening, within 30 min of tissue excision. Six patients underwent lobectomy and one patient had multiple needle biopsies of tumour and peritumoral tissue. The excised specimens were rapidly enclosed in "cling film" and transported to the adjacent laboratory for measurement of brain water content.

Imaging

All patients were scanned the day before surgery with the M&D 800 NMR Imager at the Royal Infirmary, Edinburgh (Smith et al, 1984). For each section an interlaced saturation-recovery and inversion-recovery pulse sequence was used with a repetition time of 1 s for both, and in the latter a T_1 (time to inversion) of 200 ms was used. The slice thickness was 12 mm and the acquisition time 4 min 16 s. A calculated T_1 image was obtained from the saturation-recovery and inversion-recovery images using a two point method. This was felt to be adequate given that most tissues exhibit a single exponential decay curve (Ling et al, 1980). The use of an adiabatic fast passage inversion pulse ensures efficient inversion throughout the section. The mathematical algorithm used produces sufficiently accurate T_1 values (Redpath, 1982) and the long term precision of T_1 values, measured over a 6 month period, varies from 2.3% for $T_1 = 160$ ms to 4.1% for $T_1 = 500$ ms. Between four and eight sections were collected from each patient.

Brain water measurements

Brain water content was measured by microgravimetry using small tissue samples from the lobectomy specimens. The specific gravity (s.g.) of each sample was determined by placing it in a layered gradient column of a mixture of kerosene and bromobenzene oil, that had a high specific gravity at the bottom and a low specific gravity at the top (Marmarou et al, 1978). Two minutes after insertion of the sample into the column, its depth in the oil was measured, and the column was subsequently calibrated by measuring the depth of potassium-sulphate droplets of known specific gravity. The water content of each sample was then calculated from its specific gravity using the formula:

$$\text{g water/g tissue} = 1 - \frac{\text{sample s.g.} - 1}{(1 - 1/\text{solids s.g.}) \times \text{sample s.g.}}$$

derived by Nelson et al (1971). The s.g. of the normal human cortex and white matter solids was determined by wet-weighing 500 mg samples from five patients with normal brain in their operative specimens, and then reweighing the same samples after drying to constant weight at 80°C (Nelson et al, 1971).

The lobectomy specimens were sectioned in the transverse plane. Three samples of peritumoral white matter, each weighing about 10 mg, were taken from each site. Each sample was measured in the layered kerosene/bromobenzene density column (Marmarou et al, 1978), and samples of normal cortex and white matter, when present in the specimen, were similarly measured. In two patients, macroscopically oedematous cortex was also sampled. All gravimetric measurements were completed within 15 min of excision of the specimen, to minimise water loss from the tissues. The lobectomy specimen was then fixed for subsequent histological examination.

Analysis

The NMR images were reviewed by the same radiologist and surgeon without reference to the gravimetric data. The sites of tissue sampling had been noted by the surgeon with reference to known landmarks. T_1 values for abnormal tissue were obtained from those sites using the region of interest facility on the diagnostic console. Values for normal tissue were taken by the same method, wherever possible, within the lobe which had been resected.

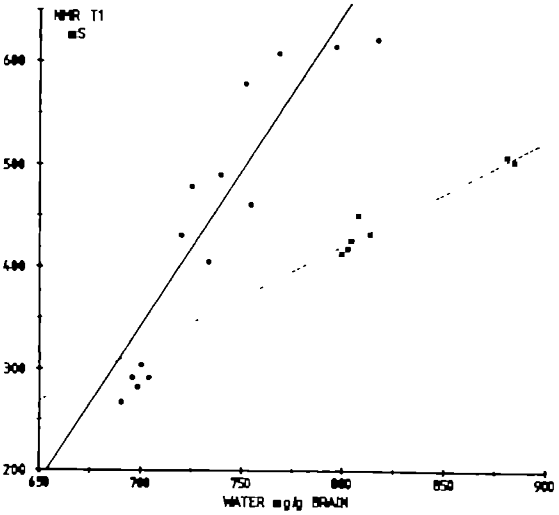

FIG. 1.

Graph of water content and NMR T_1 values for cortex and white matter. – – – – Linear regression line for normal and abnormal cortex (no mannitol □, with mannitol ■). ——— Linear regression line for normal and abnormal white matter (no mannitol ○, with mannitol ●)

RESULTS

A graph of T_1 values plotted against brain water readings for normal and oedematous tissue is shown in Fig. 1. A significant correlation exists between the two measurements for white matter ($r = 0.92$, $P < 0.001$), and cortex ($r = 0.97$, $P < 0.001$). Statistical analysis of the data (Smith et al, 1981) demonstrates that the errors of the techniques account for the spread of the bivariate data about the regression line ($\chi^2 = 36.9$, $P < 0.001$).

DISCUSSION

Brain tumours are often surrounded by a zone of oedema. This form of oedema is regarded by Klatzo (1972) as vasogenic, where oedema fluid emerges through a defective blood-brain barrier and spreads in the extracellular space of the white matter. This preliminary *in-vivo* study confirms in patients with brain tumours the linear correlation between brain water content and NMR T_1 values, previously reported in experimental animal models. Our results, however, highlight differences between white matter, where T_1 increases rapidly as water content rises, and cortex, where the increase is slower. In normal tissue the water content of cortex is greater than that of white matter, our finding of 10% agreeing closely with the 10–15% reported by other authors (Mathur-De Vré, 1984). The T_1 of normal cortex is correspondingly longer than that of normal white matter. Oedema fluid accumulating in cortical tissue is taken up by the cells and is, therefore, influenced by the intracellular macromolecules. The water protons are "bound" in the hydration layer around the macromolecules and this alteration in their dynamic state shortens their relaxation time (Mathur-De Vré, 1984). In oedematous white matter more water remains in the extracellular compartment. A lower rate of collisions between molecules in this "free" state results in a longer relaxation time. Previous authors, working with rat brain *in vitro,* have attributed the linear increase in T_1 with water content to increase in the "free" water (Go & Edzes, 1975). Although results from our small sample must be interpreted with caution, we have shown a less marked rise in cortex, in keeping with the smaller rise in "free" as opposed to "bound" water. It appears that NMR T_1 values can be used to predict the degree of cerebral oedema in white matter, and possibly in cortex.

Four of our patients received intra-operative mannitol. Measured water content in their peritumoral white matter is lower than might be expected from pre-operative T_1 readings. Magnetic resonance imaging may prove a useful tool in assessing the effect of mannitol and other agents on cerebral oedema.

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Book reviews

Radionuclide Imaging of the Brain By B. Leonard Holman, pp. xiv+232, 1985 (Churchill Livingstone, New York), £60 00
ISBN 0-443-08348-7

This is a superb book. It is a multiauthor text, comprehensively covering the uses of PET, SPECT, dynamic SPECT and iodine 123-labelled amines for brain imaging, quantitation of regional cerebral blood flow together with excellent reviews of conventional brain and CSF imaging with, at all times, emphasis on clinical application All chapters are extremely well written and the book is a pleasure to read, although expensive at £60

This book will be of interest to all workers in nuclear medicine, but its practical value is limited, as positron tracers are available to very few due to the phenomenal cost and expertise required to maintain a cyclotron, related equipment and a radiochemical laboratory. Further, since the advent of CT scanning, the conventional brain scan is no longer one of the more commonly performed investigations in nuclear medicine departments There is, however, increasing interest in the use of radiotracers to study functional processes in the brain. The timing of this book is, therefore, unfortunate as it has missed out on the most exciting development to occur in brain imaging for many years. Although it was hinted that ^{99}Tc^{m} perfusion agents may well become available in the near future, this has now become fact with the introduction of ^{99}Tc^{m} hexamethyl-propyleneamine oxime (HM-PAO). Excellent papers on this topic were presented at both the Society of Nuclear Medicine Meeting in Houston and the European Congress in London this year I would predict that this new agent, although still under evaluation, will soon become firmly established in clinical practice and will replace the use of iodoamphetamine.

Radionuclide Imaging of the Brain is a highly recommended book and certainly should be available to all nuclear medicine departments as a source of reference

I Fogelman

Angiographic Anatomy of the Anterior Inferior Cerebellar Artery By J. J. Heimans, J Valk and A. H. M. Lohman, pp. vii+91, 1985 (Springer Verlag, Berlin, Heidelberg, New York, Tokyo), DM 58
ISBN 3-540-13768-8 Berlin
0-387-13768-8 New York

This is a satisfactory monograph, especially in so far as it describes and illustrates, with beautifully designed and produced line drawings, the normal anatomy of the anterior inferior cerebellar artery (AICA) and related vessels The descriptive and discursive text is comprehensive the drawings have been made after dissection of 20 "normal" patients who died "non-cerebral" deaths.

The last half of the book discusses the AICA in normal and abnormal vertebral angiograms and illustrates them from an analysis of 100 cases. These pictures are crisp and well documented, if a trifle small. There is a good bibliography and an effective index.

This is a book for neuroradiologists in training to read with care, and for the neurosciences reference library

G. H du Boulay

1986, *The British Journal of Radiology*, 59, 359–363 APRIL 1986

Radiation doses and somatic risk to patients during cardiac radiological procedures

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ABSTRACT

The radiation dose to a series of adult and paediatric patients undergoing cardiac catheterisations and adults having percutaneous transluminal coronary angioplasty has been measured/determined directly using lithium fluoride thermoluminescent dosemeters and indirectly using an air ionisation chamber which indicated exposure-area product Somatic and genetic risks are estimated from the dosimetry results It is suggested that the magnitude of the radiation hazard is negligible compared with other clinical hazards associated with these procedures.

It is well known that high radiation doses to the patient result from cardiac catheterisations carried out under fluoroscopic control. Scattered radiation dose to the thyroid has been studied by a number of authors (Kaude & Svahn, 1974; Rowley, 1974). Later work also included gonadal doses (Martin & Olsen, 1980). Another approach to determining patient doses involves measurements of exposure-area product (Rcm^2) during cardiac radiological procedures (Kaude & Svahn, 1974; Rowley, 1974, Gustafsson & Mortensson, 1976).

Modern equipment with a U-arm mount for both the X-ray tube and image intensifier has been introduced since these earlier surveys. As cardiac radiological techniques have also changed with the introduction of this new design, it was decided to carry out a new study involving both adult and paediatric patients undergoing cardiac catheterisations. In order to compare the results of this new study with previous work, it included measurements of both exposure-area product and scattered radiation dose to a number of organs. This dosimetry information will also enable an assessment of any future changes in either radiological equipment or examination technique to be made.

Percutaneous transluminal coronary angioplasty (PTCA) is a recently introduced method of clearing obstructed coronary arteries. Since long screening and cinefluorography times are associated with this technique, high radiation doses to patients may be expected Consequently, it was decided to determine the radiation dose to patients undergoing this procedure.

In common with other radiological examinations there is inevitably a certain degree of risk associated with the use of ionising radiation. The patient dosimetry results have been employed to estimate the somatic and genetic risks from the radiation dose resulting from cardiac catheterisations and angioplasties.

MATERIALS AND METHODS

All cardiac radiological investigations were performed on equipment with an undercouch tube/overcouch image intensifier configuration. The image intensifier had two input field sizes (22 cm and 15 cm) and both operated under automatic exposure-rate control (exposure-rate in air at image intensifier surface 50 μR/s) Under automatic exposure-rate control, both the tube potential and tube current were adjusted to maintain a constant exposure-rate at the input surface of the image intensifier. Typical technique factors for adults were in the range 70–110 kV and 1.4–7 mA. The corresponding technique factors for paediatric patients varied between 65 and 85 kV, and 0.5 to 1.1 mA. Cinefluorography was also performed with a pulsed X-ray output at 50 frames/second (exposure 24 μR/frame). Automatic exposure and brightness control were employed during cinefluorography which, for adult patients, resulted in a tube potential in the range 70–120 kV and a tube current of 180–720 mA. For paediatric patients the corresponding technique factors were 65–85 kV and 130–260 mA. At the end of each examination a note was made of the total fluoroscopy and cinefluorography times.

Radiation doses were measured at a number of anatomical positions using lithium fluoride thermoluminescent dosemeters (TLDs). A calibration factor for the range of diagnostic beam qualities used was experimentally determined and applied to the dosemeter readings. Dosemeters were attached to the patient using surgical tape at the following anatomical positions:

(1) xiphisternum,
(2) right mid-auxillary line at level of xiphisternum,
(3) left mid-auxillary line at level of xiphisternum,
(4) spinous process of ninth thoracic vertebrae,
(5) thyroid,
(6) iliac crest, and
(7) thigh (not children).

The last two dosemeters were used to monitor gonadal doses.

TABLE I

SUMMARY OF SCREENING AND CINEFLUOROGRAPHY TIMES

Type of dosemeter	Examination	Number of patients	Screening time (min)			Cinefluorography time (s)		
			Mean	Standard deviation	Range	Mean	Standard deviation	Range
Thermoluminescent dosimetry (TLD)	Adult catheterisations	8	7.2	3.0	3.0–12.0	53	22	37–79
	Paediatric catheterisations	7	6.0	3.1	2.6–10.6	22	19	5–60
	PTCA	15	26.9	16.7	8.7–69.5	58	31	25–158
Exposure-area product	Adult catheterisations	17	6.3	3.5	1.6–12.6	53	18	25–92
	Paediatric catheterisations	6	6.4	1.7	4.2– 9.2	25	16	0–55
	PTCA	7	29.5	19.9	10–69.5	46	16	37–75

After irradiation the exposed dosemeters were attached to a specially designed form on which the age and sex of each patient was recorded.

Initially, all dosimetry measurements on the angioplasty patients were performed using TLD, although for later patients a transparent ionisation chamber (PTW Diamentor System) attached to the X-ray tube was used in addition. This ionisation chamber measured exposure-area product and had been calibrated for these X-ray energies prior to use. The patients (both adult and paediatric), who had cardiac catheterisations, were monitored with only one type of dosimetry method, initially with TLD and later using the Diamentor. No patients having cardiac catheterisations were monitored using both methods.

The Diamentor measurements of exposure-area product were converted into energy imparted (in J) using data presented by Shrimpton et al (1984). This conversion requires a knowledge of both the X-ray tube applied potential and the total filtration of the X-ray beam, which was estimated from the half-value layer measurement at a measured tube potential and was equivalent to 3.4 mm aluminium.

RESULTS AND DISCUSSION

A summary of the number of patients monitored, the average screening and cinefluorography times for each type of investigation, is given in Table I. It may be seen from this table that the respective screening and cinefluorography times are similar for the same examination using both types of dosemeters. The screening times during angioplasties are much higher than adult catheterisations, which reflects the difficulties attendant in manoeuvering the guide wire and balloon catheter into position during the former procedure. Perhaps future developments in the design and construction of guide wires and balloon catheters will reduce screening and cinefluorography times, thereby reducing the radiation dose to both patients and staff.

Table II is a summary of the dosimetry results for all patients monitored. The mean, standard deviation, and range of both the Diamentor reading and the doses measured at each separate position are included in this table. The total of the four chest-level dosemeters has also been quoted, as this will partially account for changes in projection direction. During the course of some of the examinations, patient movement caused one or other of the TLDs to become detached from the patient. Consequently these dosemeters were excluded from the study, which meant for some patients it was impossible to determine the total of the four dosemeter readings. Hence there is a discrepancy between the mean of the total of the four dosemeters and the total of the four means for each position at chest level.

The mean value of exposure-area product was 490 Rcm^2 for paediatric cardiac catheterisations, which is similar to that reported in an earlier study (Rowley, 1974), but slightly higher than that quoted in another study (Gustafsson & Mortensson, 1976) for children aged between 1 and 13 years, which is similar to the age range of the patients monitored here.

The mean exposure-area product for adult cardiac catheterisations was somewhat higher than had been previously measured (Ardran et al, 1970; Rowley, 1974). Both the dose-rate in air at the image intensifier input surface and the dose per frame during cinefluorography were within an acceptable range. Given that the average screening times were shorter than in an earlier study (Ardran et al, 1970), then the increase in measured exposure-area product must arise from considerably longer cinefluorography times. As cinefluorography is a major contribution to patient exposure in cardiac catheterisations, due to the high dose-rate, any attempt at patient dose reduction should be concentrated on this side of the examination.

Mean measured exposure-area product readings are similar for angioplasties and adult catheterisations, although the range of readings is far greater for

TABLE II

Summary of dosimetry results (mGy)

Dosemeters	Adult cardiac catheterisation			Paediatric cardiac catheterisation			PTCA		
	Mean	Standard deviation	Range	Mean	Standard deviation	Range	Mean	Standard deviation	Range
Total of four trunk dosemeters	59.2	40.8	21.1–127.1	66.3	57.9	5.2–145.7	151.9	76.0	50.6–298.1
Xiphisternum	5.9	4.6	2.8– 15.3	4.2	4.9	0.3– 13.7	10.5	7.0	2.8– 26.7
Right mid-auxillary line	20.3	23.8	1.4– 98.8	20.8	24.2	0.1–119.7	75.7	85.6	0.6–280.7
Left mid-auxillary line	13.8	9.3	2.8– 25.7	4.4	5.0	0.2– 12.2	4.7	4.4	0.6– 18.1
Spinous process T9	19.4	32.8	3.6– 75.9	37.0	45.5	4.6– 73.5	55.1	64.6	3.3–200.7
Thyroid	1.7	0.8	0.8– 2.7	1.2	1.3	0.2– 3.7	2.0	0.9	0.8– 4.1
Iliac crest	0.4	0.3	0.1– 0.9	0.7	0.7	0.0– 1.8	1.2	1.1	0.0– 3.2
Thigh	0.1	0.1	0.1– 0.2	—	—	—	0.3	0.2	0.0– 0.8
Diamentor reading (Rcm^2)	4800	3010	180–12 500	490	360	150–570	3270	1440	2320–5780
Energy imparted (mJ)	473.0	296.8	17.7–1232.6	42.9	31.5	13.1–49.9	322.5	142.0	228.8–570.0

catheterisations. Average screening times are longer for angioplasties when compared with adult cardiac catheterisations, but the cinefluorography times are approximately equal. Thus, as the mean measured exposure-area product is lower for angioplasties, it would imply that larger field sizes are employed in adult cardiac catheterisations.

For all three types of investigation, the total of the four trunk dosemeter readings was considerably less than that estimated from the average exposure-area product and the area of the X-ray field. In general, each procedure involves the use of many projections. There will not be a dosemeter in the primary beam, except for the PA and lateral projections. It is impractical to use extra dosemeters, as a large number would be necessary without an advance knowledge of the projection directions to be used. The overall effect of a multiplicity of projection directions is to reduce the maximum skin dose at a point, as there is a considerable difference in skin-dose distributions for these projections.

The radiation doses to the other three sites arise from scattered radiation, as these dosemeters were placed on the exit side of the patient, and the effect of any tube leakage radiation on the readings will be negligible. The surface dose will therefore be a good indicator of the dose to the corresponding organ within the body. The radiation dose to the thyroid for both adult and paediatric catheterisations, given in Table II, is considerably lower than that stated in other publications (Gustafsson & Mortensson, 1976; Martin & Olson 1980). Whilst the thyroid dose during angioplasty is higher than for both adult and paediatric cardiac catheterisations, it is still lower than the thyroid dose quoted in the above publications.

In the main, the radiation dose to both the ovaries and testes during adult and paediatric cardiac catheterisations quoted in Table II compare favourably with previously published results (Gough et al, 1968; Kaude & Svahn, 1974; Langmead & Wall, 1976; Martin & Olson, 1980). Gonadal doses during angioplasty are approximately three times higher than the dose received by adult patients having cardiac catheterisations. Higher gonadal doses will arise from differences in the cardiologist's technique, as the movement of the guide wire and balloon catheter from the femoral artery to the heart will be observed in angioplasty using fluoroscopy.

Also quoted in Table II are the calculated values for the energy imparted during each type of investigation, as the energy imparted correlates with the total somatic risk. The energy imparted has been calculated from the Diamentor reading using previously published factors (Shrimpton et al, 1984).

Patients having an angioplasty will, in general, also have at least two cardiac catheterisations—one before the angioplasty and one 6 months after as a follow-up. Consequently, when assessing the total dose to a patient having an angioplasty, the contribution from two cardiac catheterisations should also be included.

Somatic and genetic risk factors have been published by the International Commission on Radiological Protection (ICRP, 1977). The risk factors averaged for males and females over all ages have been employed to calculate risks. In this study a genetic risk factor of 4×10^{-3} Sv^{-1} has been used for adults, which is an average over all the population and refers to the effect manifest in the first two generations, whilst for paediatric patients a factor of 1×10^{-2} Sv^{-1} was employed, since it is assumed that all such exposures were genetically significant. Genetic risks were estimated by multiplying the mean ovary and testes dose by the above genetic risk factor. For paediatric patients, testes dose was estimated from the dose to the

TABLE III

ESTIMATED SOMATIC RISKS (FATAL MALIGNANCIES PER EXAMINATION) × 10^{-6} AND *GENETIC RISKS × 10^{-6}

Risk	Adult cardiac catheterisation	Paediatric cardiac catheterisation	PTCA
Leukaemia	8	2	5
Bone cancer	2	<1	1
Breast cancer	15	11	26
Lung cancer	31	6	21
Thyroid cancer	<1	1	1
Other cancer	2	2	2
Total somatic	59	22	56
Genetic: male*	1	2	1
Genetic: female*	2	7	5
Total somatic risk from energy imparted	132	12	90

(*Risk of serious hereditary ill health in the first two generations per examination)

iliac crest. The results of these calculations for the three investigations studied are given in Table III.

Thyroid cancer risk was directly determined by multiplying the dose by the risk factor. Breast cancer induction was estimated by multiplying the dose to the sternum by the risk factor, which assumes that the dose to the sternum is a good approximation to the average breast dose.

The dose to the active bone marrow was calculated from the exposure-area product measurement using a previously published expression (Bengtsson et al, 1978). This value was then employed to calculate the risk of leukaemia and bone cancer (see Table III). Whilst the distribution of the two tissues concerned is dissimilar, for the purposes of these calculations the above approximation will be reasonably accurate, as the overall magnitude of the risks will be dominated by the fraction of those organs lying within the directly irradiated volume.

An average dose to the lungs was deduced from the exposure-area product, the average field size, and the estimated average attenuation in the thorax Somatic risk was then estimated from this figure.

The somatic risk to the remaining tissues which, except for the oesophagus, lie in the abdomen, was estimated from either a dosemeter reading or the exposure-area product, the average field size and an appropriate normalised organ dose value (Rosenstein et al, 1979; Gray et al, 1981). Where applicable, an allowance was made for the difference in field size during these cardiac radiological procedures from those quoted in the above publications. The results of these calculations are given in Table III.

It is possible to estimate the somatic risk from the energy imparted by using the factor (0.28 kJ^{-1}) proposed by Wall and Shrimpton (1981). The results of these calculations, included in Table III for comparison, correlate with the risk factor approach, within the anticipated accuracies of the two techniques.

In summary, Table III shows the estimated somatic and genetic risks from the three types of cardiac radiological procedures studied. The data in this table have been rounded to the nearest integer; consequently there may be a discrepancy between the total somatic risk and the sum of the separate risks for certain investigations. It may be seen from this table that the total somatic risk is dominated by the breast and lung cancer induction. Thus, the uncertainty in the total somatic risk will be governed mainly by the accuracy of the assumptions made in estimating these organ doses and by the risk factors employed. It is anticipated that the organ doses are accurate to within a factor of 2. The uncertainty in the risk estimates will be due mainly to the incomplete knowledge of risk factors, and whether they are strictly applicable to this select population. The risk estimates quoted in Table III are meant to be an approximate guide to the radiation hazards associated with these procedures.

CONCLUSIONS

The radiation dose to a number of organs and the exposure-area product for a series of patients undergoing cardiac catheterisations and angioplasty have been monitored. These data, together with both somatic and genetic risk factors, have been employed to estimate the radiation risk from cardiac radiological procedures. The total somatic risk was estimated to be between 59×10^{-6} and 132×10^{-6} for adult catheterisations, between 12×10^{-6} and 22×10^{-6} for paediatric catheterisations, and between 56×10^{-6} and 90×10^{-6} for PTCA. In general, a patient having an angioplasty will have one catheterisation for diagnosis prior to angioplasty and one afterwards for follow-up purposes. The total somatic risk for these three investigations lies between 174×10^{-6} and 354×10^{-6}. There is a considerable uncertainty associated with these risk estimates, mainly due to incomplete knowledge of the risk factors for this group of patients. In any case, the somatic and genetic risks are negligible when compared with the other clinical risks associated with these procedures.

ACKNOWLEDGMENTS

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Book reviews

Cardiac Imaging and Image Processing. Ed by S. M Collins and D. J Skorton, pp xii+425+index, 1985 (McGraw-Hill, Maidenhead), £60.00.
ISBN 0–07–057921–1

The heart poses particular challenges to those who develop the techniques of diagnostic imaging In this volume the editors have drawn contributions from 28 scientists from a variety of disciplines to present in some detail the techniques of echocardiography, X-ray digital cineangiography, positron emission tomography and magnetic resonance imaging, each as applied specifically to cardiac imaging The first chapters in the book provide a well written and thorough presentation of these important techniques which would serve as an excellent general teaching text, with adequate but not excessive mathematical bias. In addition, a variety of processing algorithms for smoothing, edge detection, spatial warping and parametric imaging are discussed in detail. The remaining chapters describe the specific cardiological applications Some chapters, such as those on PET or high-speed CT, will be of academic interest to most readers, though none the less fascinating for that I was sorry to find the PET image plates missing in the review volume, since the intercomparison of cardiac images within a single volume is particularly valuable. Throughout, there is a good balance between clear technological presentation, with well drawn diagrams, and statements of the clinical goals and objectives of diagnostic cardiology Each chapter is well referenced. However, it will be of practical interest primarily to those who have very substantial financial resources. We are told that the Mayo DSR may gather 480 MBytes of data from only one second of scanning, up to 100 times greater than the data rate from LANDSAT III! Neither here, nor in the useful intercomparison of the various methods, are costs or clinical cost-effectiveness considered.

This book provides a fascinating and clear insight into the most technologically advanced techniques for cardiac imaging, and would enhance any reference library It would seldom be of value in the clinical work of the majority of non-academic departments

F A DUCK

A Guide to Cardiac Ultrasound. By Robert M. Donaldson and Caroline Westgate, pp vi+94+index, 1985 (King and Wirth Publishing Co., London), £6.50
ISBN 0–048306–02–5

The authors of this small paperback book have made a valiant attempt to survey the whole subject of cardiac ultrasound in less than 100 pages The book is well produced and there are many good illustrations. All relevant major disease categories in cardiology are mentioned but, in some cases, the mention is little more than a listing. The entire field of congenital heart disease is, for example, described in one page of text and a mixed collection of illustrations. Prosthetic heart valves are covered in even less space.

The important field of Doppler echocardiography is represented but oversimplification has led to possible misunderstanding. Many capabilities of this technique are described without consideration of the many pitfalls and potential errors that can be made. This simplistic approach is also evident in other areas An example of this is the description of left ventricular measurement by M-mode and cross-section echocardiography. The uninformed reader would assume this to be very simple but experience in the field would show this to be otherwise.

The main function of this interesting book will be to outline the current capabilities of cardiac ultrasound for those not directly engaged in its practice It cannot be more than an introductory handbook for any who actively intend learning the techniques.

I am disappointed that the foreword and preface of this book indicate that only physicians and cardiologists are involved in cardiac ultrasound scanning. Perhaps the authors are unaware of the significant and increasing number of radiologists undertaking this type of ultrasound investigation

PETER WILDE

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A method for increasing the resolution of scanned projection radiography and other digital X-ray systems

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ABSTRACT

A method for increasing the sampling frequency of digital X-ray systems is described. The method employs discrete, stepwise magnetic deflection of the focal spot and the recombination of the resulting displaced images. The technique was applied to a GE CT/T 8800 scanner operating in "Scout View" mode. The hardware and software modifications were minor. The transverse resolution was shown to improve from 0.63 to 0.9 line pairs per mm, using a test phantom. The effect of the improvement in resolution is also illustrated in the human The possibility of further improving the resolution of the system is discussed.

This paper describes the development of a method for increasing the sampling frequency of digital X-ray detector systems by deflection of the X-ray focal spot. The aim is to demonstrate that an increase in spatial resolution of digital images can be obtained using simple software and hardware modifications on a commercial CT scanner The method was implemented using the scanogram, a line-scanned digital radiographic facility usually employed to locate axial sections. The good contrast resolution of some scanogram systems (Sommer & Brody, 1982) has stimulated a general interest in their direct use for diagnosis. Initial results were disappointing (Lawson et al, 1980; Baker, 1981) but with modifications more encouraging data have been obtained (Foley et al, 1979, Cassel et al, 1981).

A limitation of the scanogram is its poor spatial resolution. An increase in resolution would provide useful diagnostic images, particularly in limbs, the head, and the spine, where movement is not a problem. Transverse and longitudinal resolution in scanograms is controlled by different factors (Katragadda et al, 1979). In our study the transverse sampling frequency and spatial resolution were increased by electron-beam deflection. To increase resolution in the longitudinal direction, the X-ray beam was collimated and the interpulse cradle travel reduced. These techniques are described and high resolution images are presented.

MATERIALS AND METHODS

All experiments were performed on a GE CT/T 8800 scanner in scanogram, *i.e.* "Scout View" mode. Attaching prototype magnetic coils to the X-ray generator required a minor hardware modification. All images were produced using a standard Maxiray 100 X-ray tube The machine was in full-time clinical use and the high resolution facilities were introduced without major disruption.

High contrast spatial resolution was measured with a 0.1 mm thick lead-bar phantom. This phantom offered a convenient visual assessment of resolution in the range of 0.5 to 5.0 line pairs per mm (lp/mm). Initially it was used to estimate normal scanogram resolution in the transverse and longitudinal directions. These measurements were obtained on separate scanograms with the phantom mounted on the patient cradle in the centre of the field. For transverse measurements the lead bars in the phantom were aligned parallel to the scanner axis, whilst for the longitudinal measurements they were at right angles to it.

Increasing the transverse resolution

The principle of the technique involves discrete deflections of the focal spot. These deflections move the X-ray image in small steps across the effectively stationary detectors. A digital line image is recorded for each position of the focal spot. Recombination of two or more spatially displaced images then results in improved resolution The size of the steps between the positions of the image is manipulated such that they are a fraction of the detector width for the geometry of the selected object plane.

To increase the transverse resolution we considered a horizontal plane in the centre of the image field of the scanner 780 mm from the focal spot and 320 mm from the central detector. For simplicity, we considered first a focal-spot deflection of 1 46 mm at the anode surface, which would produce an image shift of half a detector width (0.6 mm) Other deflections may be treated by a simple extension of the geometry.

Lateral beam deflection for the image plane was equivalent to lateral displacement of the curved detector array. Out-of-plane tomographic blurring was ignored, since for a slice effectively 400 mm thick the blurring extends over less than 0.12 mm, or only 10% of the detector width. The intensity distributions sampled by the detectors are thus effectively the same for the different positions of the focal spot.

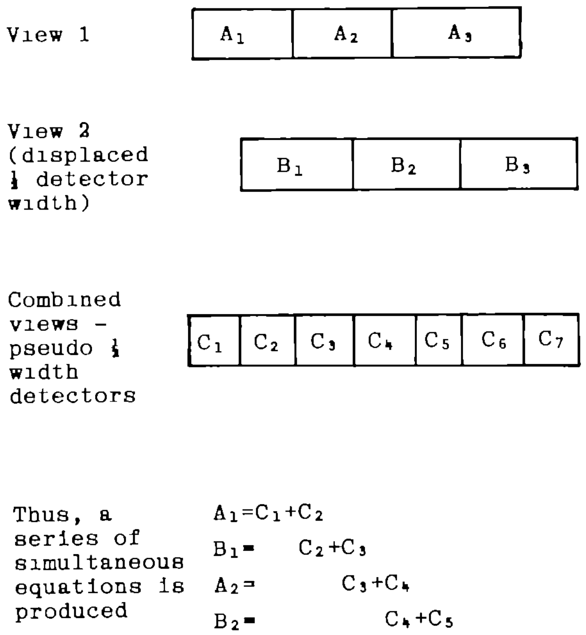

View 1
A1
A2
A3
View 2 (displaced ½ detector width)
B1
B2
B3
Combined views - pseudo ½ width detectors
C1
C2
C3
C4
C5
C6
C7
Thus, a series of simultaneous equations is produced
A1=C1+C2
B1= C2+C3
A2= C3+C4
B2= C4+C5

FIG 1.

Pseudodetector response When a detector with a rectangular response function is displaced laterally between two radiographs of the same object, the two responses A_i and B_i can be recombined to form a set of pseudodetector responses C_j These pseudodetectors have half the width and therefore twice the sampling frequency of the original detector array

The focal-spot intensity structure was assumed to be Gaussian (Barrett & Swindell, 1981) This form has previously been used to describe the GE CT/T 8800 focal spot in investigations of the resolution of CT scanners (Glover & Eisner, 1979; Blumenfield & Glover, 1981). The xenon gas detectors were each considered to have an approximately rectangular response function across a width of 1.2 mm.

In the image reconstruction pairs of detector readings were combined to produce pseudodetector values, as shown in Fig. 1. The result is a series of simultaneous equations relating m pseudodetectors to the n detector values. For simplicity, we consider recombination of two images ($m = 2n$) displaced relative to each other by half the width of a detector, thus:

$$A_i = C_j + C_{j+1}$$

$$B_{i+1} = C_{j+1} + C_{j+2} \qquad (1)$$

where A_i and B_i are the response of the ith detector and its deflected value respectively, and C_j is the jth pseudodetector value. There are several methods that can be used to solve this form of equation although image noise can invalidate direct solutions. For this study we chose a simple, locally acting iteration. This method had the advantages of simplicity and relative freedom from the propagation of noise. For each detector we set,

$$D_{i1} = A_i/2$$

and

$$D_{i2} = B_i/2$$

where D is a dummy array Then it follows that an estimate of the pseudodetector values is

$$C_j = [D_{(i-1)2} + D_{i1}]/2 \qquad (2)$$

and

$$A_i = C_j + C_{j+1} + e_{Ai} \qquad (3)$$

$$B_i = C_{j+1} + C_{j+2} + e_{Bi}$$

where e is an error term This error is calculated and distributed over the dummy array such that:

$$D_{i1} = D_{i1} + e_{Ai/2}$$

$$D_{i2} = D_{i2} + e_{Bi/2} \qquad (4)$$

After two or three iterations of the array using equations (2), (3), and (4), the image data converged. The coil produced distortion in the displaced focal spots, which necessitated the use of simple smoothing and grey-level normalisation procedures to produce artefact-free images.

Deflecting the n detectors by half a detector width is thus equivalent to sampling the X-ray intensity distribution using $2n$ half width detectors. Other possibilities, such as deflection of the spot to four positions and effectively overlapping the shifted detectors by one quarter of a detector length, involve only simple modifications to the mathematics. The technique may be used with non-rectangular detector response functions by a simple extension, but the values of the integral over the appropriate overlap regions must be known.

Recombination of images spatially separated by a fraction of the width of a single detector was modelled by the convolution of the detector response function with a comb fraction The result was convolved with the focal-spot intensity distribution to give a Modulation Transfer Function (MTF) for the system. The algorithm employed for the sampling process is essentially similar to that described by Barrett and Swindell (1981).

Coil design

The coil prototype was designed for use with the pulsed X-ray system of the scanner. This rectangular coil had 200 turns and 1 ohm d.c. resistance and was designed to fit around the initial collimator of the X-ray tube, as shown in Fig. 2. The distance between the coil centre and the electron beam was 10 cm. Current switching for the coil was triggered by the couch electronics of the scanner. These were modified to provide a pulse that reversed the polarity of the current in the coil with each X-ray pulse (25 times/s). Alternate views recorded from the xenon detector array were thus displaced by half the width of a detector.

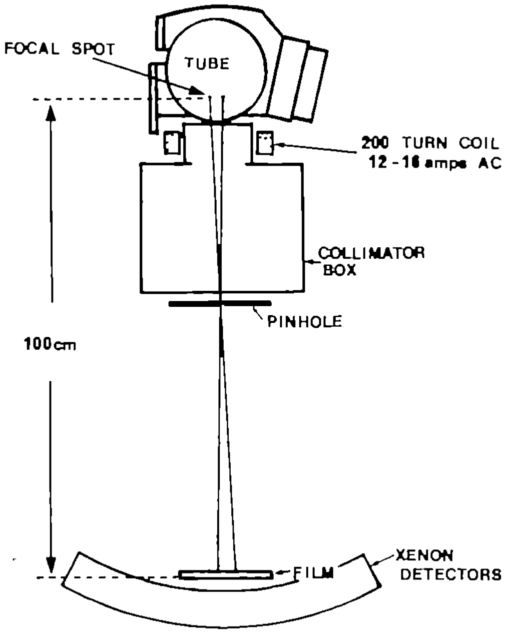


FIG. 2.

The position of the 200-turn coil, around the initial collimator box. The experimental conditions for obtaining pinhole images of the focal spot are also illustrated

A number of experiments were required initially to determine the relationship between coil current and focal-spot displacement. From this calibration the coil current required for deflection of the image by one quarter of a detector width was determined (12 A). Images obtained with focal-spot deflection were in effect double sampled.

The result of combining four laterally displaced images was investigated using a single strip of the bar phantom as the object. This phantom was positioned in the centre of the field on a travelling microscope and moved laterally in steps, each of which corresponded to an image displacement of one quarter of the detector width.

Improving longitudinal resolution

Spatial resolution in the longitudinal direction was increased by placing a 0.5 mm collimator centrally over the output of the standard collimator box. This produced an X-ray beam 3.5 mm wide at the detectors, *i.e.* substantially narrower than the 5 mm width for the normal scanogram.

A further increase in resolution was obtained by halving the interpulse cradle increment. The number of cradle-encoder output pulses for each cm of movement was doubled for the combination of the two images

Focal-spot structure

The effect of deflection on the form of the focal-spot structure was determined using the pinhole technique shown in Fig. 2. Pinhole images were recorded on dental film using 80 kVp, 320 mA, and pulse width code 3 (a 4 ms pulse width). Precise alignment for these images was achieved with simple software modifications which allowed the projection data to be read for each view. It was then possible for the pinhole or other objects to be positioned accurately over the central detector in the array. All objects placed within the scanner ring were positioned by this method

Data processing

Normal scanogram data are corrected for offsets, normalised using the reference detectors, calibrated using data from an axial air scan and filtered. For the high resolution images we employed the normal offset and reference data corrections, but used calibration data from an air scanogram instead of an axial scan. The air-calibration scanogram was carried out with the 0.5 mm collimator in place and with the coil producing lateral beam deflection. The normal scanogram low frequency suppression filter was not used.

Calibrated projections of the object were stored in scanogram raw data files. Since in each interpulse interval the cradle moved longitudinally, temporally consecutive projections were not spatially equivalent and could not be directly combined. Linear interpolation, between adjacent projection values with the same coil current direction, was therefore employed. In the final image each interpolated projection was combined with the equivalent real projection.

RESULTS

Theoretical MTF curves calculated from the Gaussian focal spot and rectangular detector response

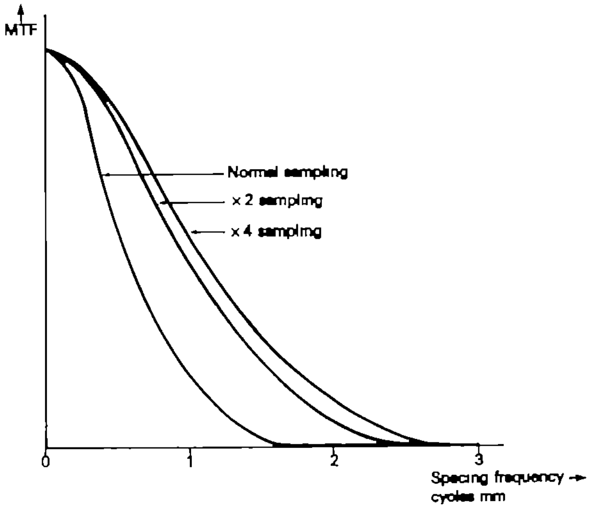


FIG 3.

System MTF curves calculated for a Gaussian focal spot and a rectangular detector response function. The curves correspond to normal, two-image and four-image recombinations.

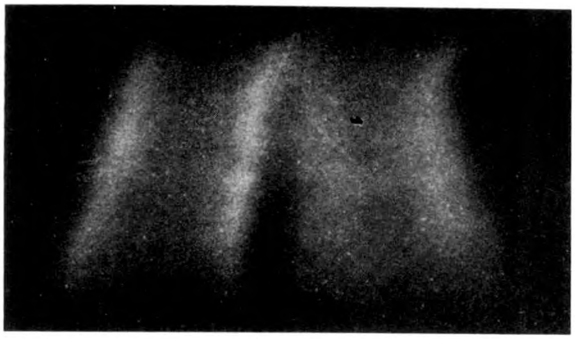


FIG. 4.
Pinhole images of the deflected focal spot obtained using the 200-turn coil.

functions are shown in Fig. 3 for normal, two-image and four-image combinations. No further improvement was obtained with eight-image combinations due to limitation by the MTF of the focal spot.

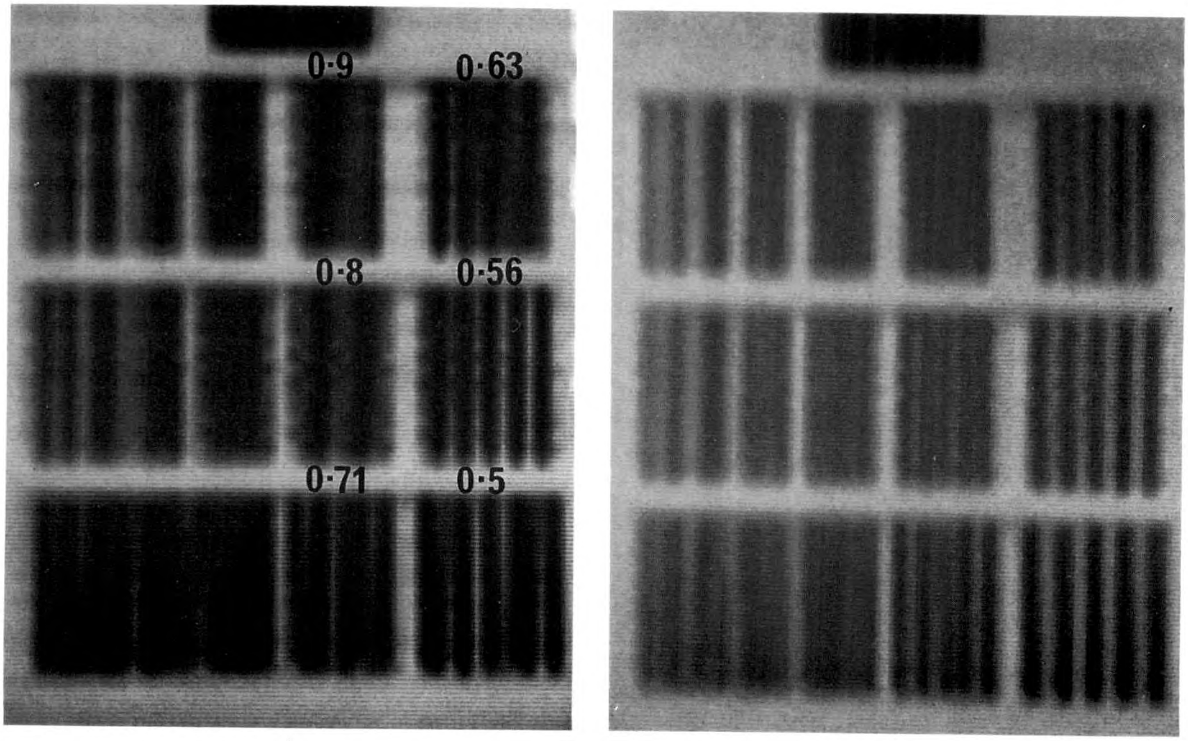
Deflected pinhole images produced by the 200-turn rapidly switching coil are given in Fig. 4. The displacement produced by this coil differed at the top and bottom of the pinhole images.

A normal scanogram and a combined image of the bar phantom, reconstructed with half-width pseudo-detectors, are shown in Fig. 5. An apparent improvement in the transverse resolution can be seen in the combined image. The four lead bars and five spaces can be resolved at 0.63 lp/mm in the normal image and 0.9 lp/mm in the improved image. This is in agreement with data derived from the predicted MTFs, which indicated an improvement of 72% in the spatial resolution.

The normal scanogram and combined image of the bar phantom, with bars aligned transversely, are shown in Fig. 6. An increase in longitudinal resolution from less than 0.5 lp/mm to 0.7 lp/mm can be seen in the combined image. Theoretically the decreased detector length should produce up to 40% improvement in spatial resolution. This appears to have been achieved.

Normal and beam deflected scanogram images of a human ankle are given in Fig. 7. The combined image is generally sharper and shows a number of features resulting from the improvement in resolution. This image demonstrates that despite the presence of substantial focal-spot distortion, artefact-free images can be produced.

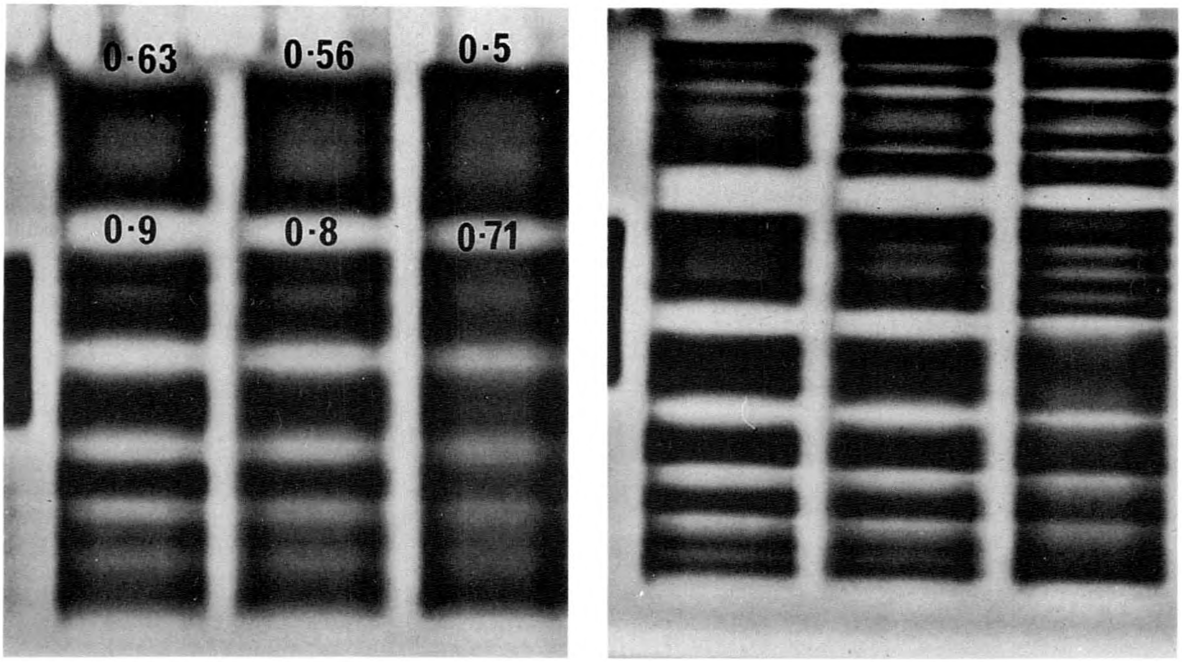
Our preliminary results from the combination of four



A

B

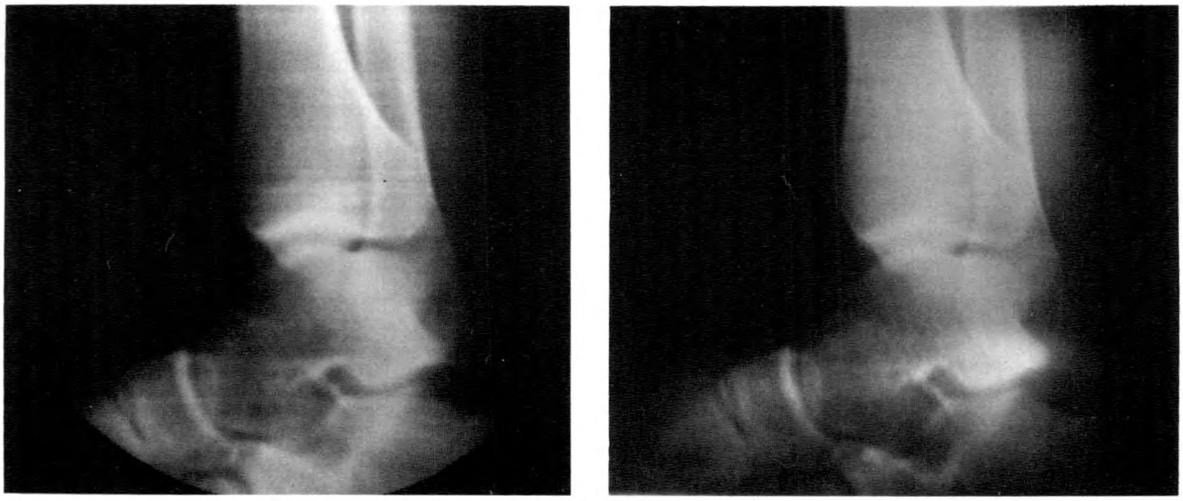
FIG. 5.
Image of lead bar phantom to show transverse resolution. (A) The normal unfiltered scanogram, resolution limit 0.63 lp/mm, (B) with electron beam deflection and image combination, resolution limit 0.9 lp/mm.



A B

FIG. 6.

Image of lead bar phantom to show longitudinal resolution. (A) Normal scanogram, resolution limit less than 0.5 lp/mm, (B) with output collimation and decreased interpulse cradle movements, resolution limit 0.7 lp/mm.



A B

FIG. 7.

(A) Normal scanogram and (B) increased resolution images of the human ankle. The images are similar but the combined image both has an improved edge definition and appears less noisy. It is clear that an acceptable image quality was obtained despite the distortion of the deflected focal spots in the prototype system.

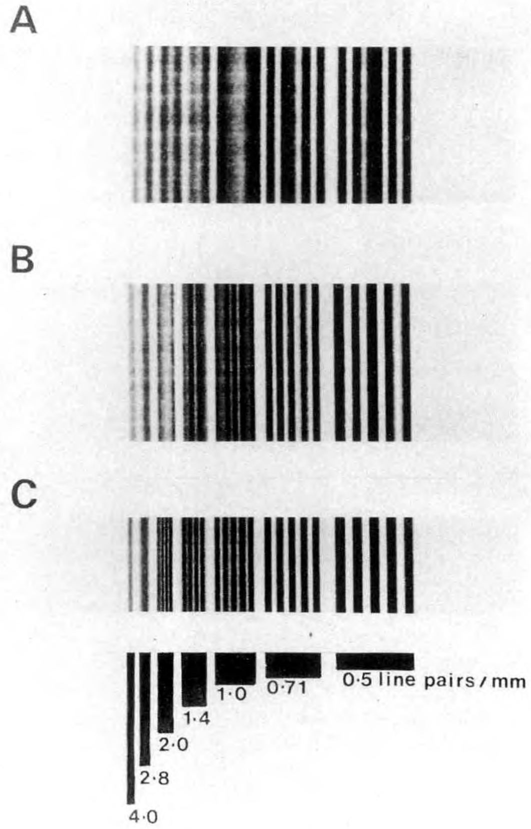


FIG. 8.

The potential of beam deflection, for further improving the resolution of a scanogram. A single strip of the bar phantom is shown with (A) single-image, (B) two-image and (C) four-image recombinations. For these images the object, not the focal spot, was moved.

images show that further substantial increases in resolution are possible. In Fig. 8 three images of the same strip of the bar phantom are shown. These images illustrate normal transverse resolution and the effect of combining two and four deflected images. These data were obtained by moving the object relative to a stationary X-ray beam. Since focal-spot distortion was not a problem in this experiment only a simple, unweighted moving average procedure was required for smoothing.

DISCUSSION

We have demonstrated that an increase in the transverse and longitudinal resolution of a scanogram system can be obtained by making relatively minor changes to a conventional CT scanner. The technique of beam deflection could have general applications in digital radiography and CT.

A specific application of beam deflection may be in digital tomosynthesis systems (Maravilla et al, 1983). In digital tomosynthesis the detector array is moved relative to the patient, and a series of images is collected. Tomographic planes within the patient are then formed by simple manipulation of the data. The techniques and algorithm described here could be applied to increase resolution.

Deflecting the electron beam, and therefore the X-ray beam, with a magnetic field is relatively simple and inexpensive. The technique can be used to achieve increased sampling frequencies, and in systems limited by detector width these modifications will improve the spatial resolution. Resolution also depends upon the intensity distribution and structure of the focal spot (Glover & Eisner, 1979). If beam deflection is employed, resolution is restricted by focal-spot size. Our results are consistent with the published analyses of oversampling (Glover & Eisner, 1979; Blumenfield & Glover, 1981), which also indicate that the increase in spatial resolution with oversampling on the CT/T 8800 is limited by the size of the focal spot. An estimate of the effective width of the detector aperture and thus the suitability of the beam deflection method may be obtained from:

$$X_{\mathrm{ef}} = [X^2+(M-1)^2S^2]^{\frac{1}{2}}/M$$

where X_{ef} is the effective detector aperture width, M is the magnification, X is the actual detector aperture width, and S the spot size (Yester & Barnes, 1977).

The disparity in transverse and longitudinal resolution, although not readily apparent in the images, could be rectified by tube and detector-box collimation. This would be an effective method for decreasing the width of the X-ray beam, but would result in wasted patient dose. Normal scanogram images do not have equal transverse and longitudinal resolution. The entry dose for a full-length scanogram is approximately 2.5 mGy, a dose which it is anticipated would be proportionately increased by decreasing the interpulse travel.

The reconstruction algorithm effectively smooths the images in the longitudinal direction and removes some of the linear artefact caused by pulse-to-pulse differences in photon flux. Pulse-to-pulse variations may be caused by deflecting the focal spot and changing the electron beam track on the anode surface (Braun, 1979). Electron-beam focusing may also be a cause, although our results suggest that non-uniformity of the applied magnetic field is the major problem. There is considerable potential in the design of coils to produce a more uniform X-ray output with alternately deflected pulses. Improved calibration procedures should reduce pulse-to-pulse variations and improve scanogram images still further.

Some focal-spot distortion was present, but it did not affect our production of higher resolution images. This distortion was not present when a larger coil, situated further from the electron beam, was used for deflection.

A computer simulation of the magnetic field in the region of the electron beam was performed. This simulation used the Bio-Savart formula (*e.g.* Kip, 1969) and involved a summation of the vector field for 600 elements of the coil wire in each of the 200 turns in the small coil, and 100 elements in each of 4000 turns in the larger coil. Non-circular geometry in the small coil wrapped round the collimator box was included in the simulation. The results indicated a 25% change in the magnitude of the field across the electron beam in the small coil and 7% with the large coil, consistent with our experimental results and the apparent cause of focal-spot distortion. Two coils, one on either side of the tube casing, could be balanced to produce a more uniform field across the electron beam.

Detector dimensions, and hence the sampling frequency, are factors which limit the resolution of many digital systems, including line-scanned projection radiographic systems (Brody et al, 1980) and CT scanners (Barnes et al, 1979). A method which achieved increased image sampling rates, and hence an improved spatial resolution, without detector or other major hardware modifications, could have widespread applications in digital radiology.

The increased resolution obtainable by combining overlapped images is limited by the focal-spot intensity distribution. This distribution is convolved with the images obtained and produces smoothing and blurring. Deconvolution in real space by direct matrix inversion (Bracewell, 1978) could provide a suitable method for removal of this focal-spot limitation.

We have shown in principle that reconstructions from four deflected images is possible as indicated in Fig. 8. Production of improved resolution images by combination of four deflected data sets is only slightly more involved than the technique used for the combination of two. The transverse resolution expected from combination of four images is close to 1.4 lp/mm. Such resolution may be sufficient for a digital alternative to conventional imaging in a number of clinical situations.

Acknowledgments

We extend our sincere thanks to Brian Pullan for his help and would like to acknowledge grants from the North Western Regional Health Authority and the Peter Kershaw Trust. We also thank I.G.E. for technical help with this study.

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Book reviews

Practical Radiotherapy Planning. Royal Marsden Hospital Practice. By Jane Dobbs and Ann Barrett, pp. xiii + 242 + index, 1985 (Edward Arnold, London), £37.50.
ISBN 0–7131–4469–6

This is a small handbook that will be of very substantial value for trainees in radiotherapy. Its subsidiary title, "Royal Marsden Hospital Practice", makes its contents clearer: it is a "recipe book" giving brief but essential details of the way most cancers are treated by radiotherapy at the Marsden. There is an 18-page introductory chapter, of which about 10 pages are taken up by illustrations, diagrams and talks, and the whole book is generously provided with these. The subsequent 32 chapters, from larynx to vagina, almost all have an anatomical diagram, usually of lymphatic spread, X-ray reproductions, many by CT scan, and the plans themselves with isodose lines. The book is very similar in purpose to the Christie Hospital, Manchester books, but is more compact; it is a very interesting contrast.

There is, however, complete absence of detail for any interstitial implants and the only brachytherapy described is gynaecological intracavitary treatment using modified Dobbie applicators, Heyman's capsules and Stockholm tubes and boxes with dosage calculated for the latter at Manchester Point A. Some detail of whole-body and half-body treatment is given but no illustrations, which could have been particularly helpful. Examples of typical field sizes would also be welcome; these also are usually not given. The dose prescribed is apparently the "tumour dose" at a specified point, rather than maximum, minimum, mean or modal: the reader is simply advised to attempt ±5% homogeneity. Corrections for tissue inhomogeneity are not discussed in any detail and one cannot be certain whether all the information obtainable from CT scans is used. Although alternative overall times and fractionation are sometimes suggested, there is no guidance on dose modification for alternatives in timing and no mention of an Ellis-type equation, TDF tables or anything similar.

These are no more than minor suggestions for improvement. All trainee radiotherapists and most of their senior colleagues should look at this book for purchase as a valuable supplement to one of the larger, more comprehensive textbooks. It is recommended very highly.

Keith E. Halnan

The Computation of Dose Distributions in Electron Beam Radiotherapy. Ed. by A. E. Nahum, pp. 342, 1985 (Umeå University, Umeå, Sweden), 150 Sw. Crowns/$20.00.
ISBN 91–7174–177–1

This book is based on manuscripts provided by lecturers who had participated at a 4-day course in 1984 in Sweden on this challenging subject. The course had been designed to give the hospital physicist an opportunity to learn about the recent developments in electron beam dose-distribution computations.

The book achieves more than this since, in addition to the section on dose computation algorithms which comprises half of the ample 342 pages, there is a section on the basic electron physics relevant to this subject.

After a short background introduction relevant to radiotherapy in general, the reader is faced with 100 pages of electron physics containing chapters by Andreo, Brahme and the editor, Nahum. This section starts with the interaction of electrons with matter and then continues with electron transport theory and the use of Monte Carlo simulation based on this. It is concluded by a review of depth-dose distributions in uniform and non-uniform media obtained from the theory described previously and from experimental results. These well written chapters are packed with clear line diagrams and are typical of the high quality maintained throughout the book. This section should provide good background material even when the algorithms described in this book have been superseded.

This is followed by the collection of lectures on dose computation algorithms which look at the limitations of the broad-beam calculations and, after covering some of the pencil-beam algorithms, there is a review of the algorithms presented in the worldwide literature and those utilised on commercial treatment planning systems. This international approach is ideally demonstrated by the occasional notation in French in a lecture by Dutreix and Briot. The book concludes by looking at the use of CT number and Monte Carlo calculations in electron beam dose-distribution calculations.

This excellent book should be compulsory reading for any hospital physicist involved in electron beam therapy.

G. Pitchford

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Report of a randomised pilot study of the treatment of patients with supratentorial gliomas using neutron irradiation

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ABSTRACT

A randomised pilot study is reported of d(15)+Be neutrons compared with 4 MV photons in the treatment of patients with astrocytoma. Sixteen patients were treated by photons and 18 by neutrons. Both treatments were well tolerated by patients The median survival after photons was 11 months and after neutrons, 7 months It was demonstrated that four of nine patients treated by neutrons had evidence at autopsy of radiation-induced brain damage All had residual cancer. No patient treated by photons had signs of radiation-related morbidity The trial was, therefore, discontinued prematurely

The treatment of patients with inoperable supratentorial gliomas is of limited value. It has been demonstrated that when X-ray therapy is given in high doses it can prolong survival and also provide useful palliation of many of the more serious effects of these tumours (Jones, 1978, Salazar et al, 1976). However, survival is poor, with a median of about 9 months in most series. The features which influence prognosis are well known. They include the histological grade of the glioma, the extent of surgical removal and the dose of radiotherapy given The age of the patient is of critical importance, patients under the age of 40–45 years having a better survival rate than older patients. Patients with major neurological disability have a much poorer prognosis than those who have minor complications (Chang et al, 1983).

Most gliomas exhibit macroscopic features of necrosis and it has been postulated that this effect may be the result of tumour hypoxia. A number of clinical studies have been conducted of techniques which, combined with X-ray therapy, might reduce the radioresistance of hypoxic cancer cells. X-ray therapy in combination with hyperbaric oxygen inhalation has been tried without any significant improvement (Chang, 1977). The hypoxic cell sensitiser metronidazole has also been used. An increase in median survival was achieved but this improvement may have been due to the change in fractionation rather than to the metronidazole (Urtasun et al, 1976). Trials using misonidazole combined with megavoltage X-ray therapy have failed to demonstrate any improvement in survival (Urtasun et al, 1977; MRC Working Party, 1983; Fulton et al, 1984).

Fast neutrons have also been the subject of investigation in the treatment of gliomas. The original studies were undertaken at the University of Washington, Seattle. Parker et al (1976a) selected patients with glioblastoma multiforme for treatment with fast neutrons. This report described the results of treating 21 patients whose survival was similar to that expected after photon therapy Autopsies were performed on seven of these patients and it was clear that their deaths were due to causes other than progressive tumour growth. They later described a syndrome of increasing neurological deterioration associated with demyelination and gliosis produced by neutron irradiation of the whole brain (Shaw et al, 1978).

Catterall et al (1980) reported on a series of 30 patients randomised to receive neutron therapy and 33 to be given megavoltage X-ray therapy. Again, survival was similar in the two groups. It was thought, on the basis of autopsy evidence, that neutrons had a greater effect on the tumours than photons. However, they also reported the syndrome of progressive dementia due to neutron-induced damage in some patients. Two neutron doses were prescribed in this trial, 15.6 Gy and 13.0 Gy, each given in 12 fractions over 4 weeks. Cerebral necrosis in regions remote from the tumour was observed in at least six out of 18 patients who received the higher dose and two of 11 patients given the lower dose. Such a high incidence of brain necrosis was considered unacceptable. For this reason a neutron dose of 12.6 Gy (13.8 Gy total dose; 9% gamma) was chosen for the randomised Phase II study carried out in Edinburgh. The results of this study are reported here.

PATIENT SELECTION

All patients had histologically confirmed supratentorial gliomas, either astrocytoma, oligodendroglioma or ependymoma, Patients were eligible for inclusion in the study if they were between the ages of 16 years and 65 years, provided that they were considered fit for a course of radical radiotherapy.

All patients had been assessed by computed tomography of the brain, with and without contrast medium, and by cerebral angiography. Informed

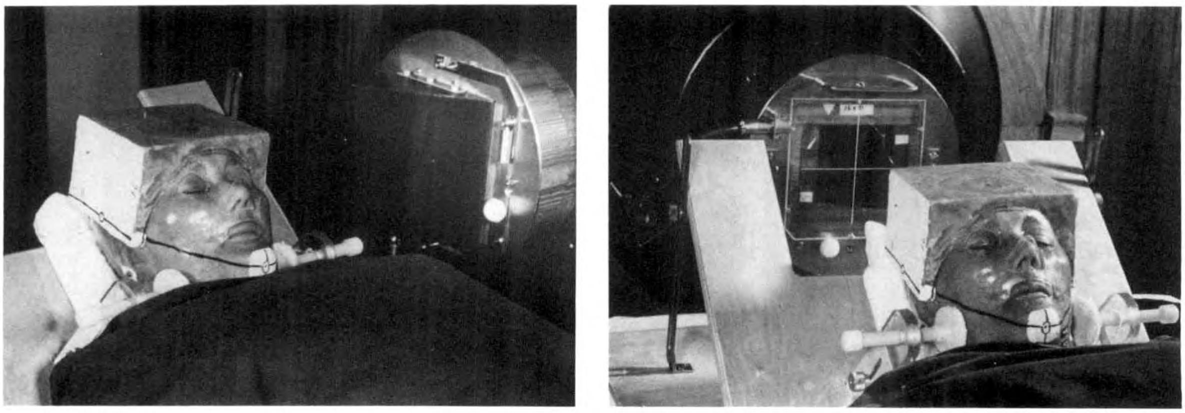

FIG. 1.

Beam-directed shell for neutron therapy: (A) lateral field; (B) vertex field.

consent was obtained from all patients. After acceptance for entry to the trial, patients were stratified by age (up to and including 40 years and over 40 years) and by tumour vascularity assessed by angiography (vascular and avascular). Patients were then allocated at random to receive neutron or photon therapy by opening sequentially numbered envelopes containing treatment options prepared by the statistician.

TREATMENT

Surgery

Nine patients treated by each modality had a biopsy only, two in each group by way of a craniotomy, the rest through a burr hole. Nine patients in the neutron-treated group and seven in the photon group had subtotal or macroscopically complete excision of the tumour.

One patient in each group also had drainage of a cyst carried out at operation. Dexamethasone was given as required, both before and after surgery, to both groups of patients.

Radiotherapy

All patients were treated by 20 daily fractions in an overall time of 4 weeks. Beam direction shells were used to facilitate the treatment positioning and to ensure the accuracy of field alignment (Fig. 1). Photon therapy was given using two lateral fields (Fig. 2) and neutron therapy using a three-field technique, with two lateral wedged fields plus a vertex field (Fig. 3). The whole brain was included in the irradiated volume.

The photon-treated patients received a target absorbed dose of 47.5 Gy, the neutron-treated patients, a total target absorbed dose of 13.8 Gy (9% gamma).

RESULTS

A total of 34 patients was entered into the study between June 1977 and October 1979. Eighteen patients were randomised to receive neutron therapy and 16 to receive photon therapy.

The distribution of patients by age, sex, tumour vascularity and neurological deficit is given in Table I. There were more females in the neutron group than in the photon group but the difference is not statistically significant. When patients were classified by degree of neurological impairment, more patients with major deficits were found in the neutron group (eight) than in the photon group (three).

The two groups contained similar numbers of patients with malignant astrocytomas (Table II). One patient in the neutron group had a tumour of low-grade malignancy, while three patients in the photon group had astrocytomas which contained elements of oligodendroglioma. It is recognised that these histological features may be associated with improved survival. There was one tumour histologically confirmed to be a pure oligodendroglioma in each group.

Only one patient failed to complete the prescribed treatment. During her neutron therapy she deteriorated in spite of being given increasing doses of dexamethasone and at autopsy was found to have an extensive necrotic malignant glioma.

All patients treated by neutrons developed complete and permanent epilation in the treated area. The patients treated by photons all developed patchy epilation after treatment; regrowth occurred but the new hair seemed finer.

One patient, treated by neutrons, was diagnosed at operation as having an ependymoma of the third ventricle extending inferiorly to involve the pituitary gland. Two months after completing neutron therapy she developed meningitis. Her condition continued to deteriorate and she died at 7 months. At autopsy and histological review it was concluded that her tumour was a chromophobe adenoma of the pituitary gland which had expanded superiorly and laterally, rather

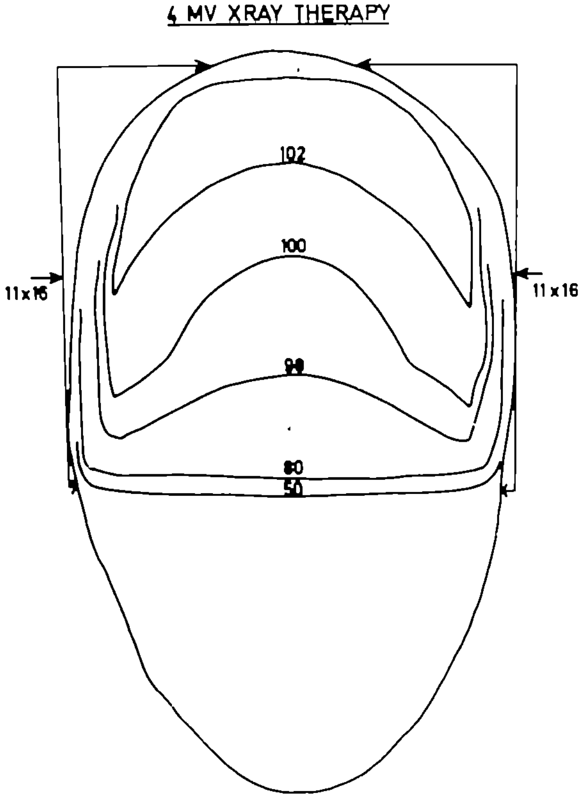

FIG. 2.
Plan for photon therapy: two lateral fields.

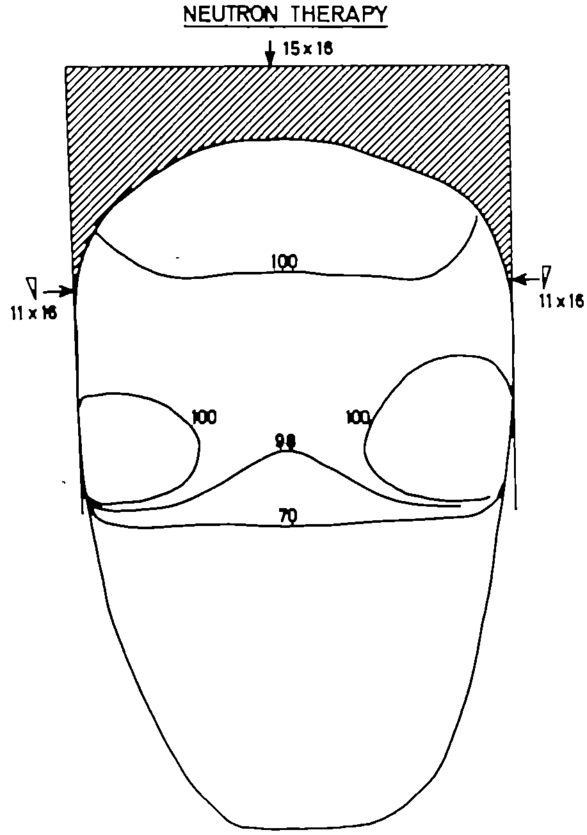

FIG. 3.
Plan for neutron therapy two lateral fields and a vertex field.

than a glioma. She is, therefore, excluded from analyses of tumour response and survival. This leaves 17 assessable patients in the neutron-treated group and 16 in the photon-treated group.

TABLE I
DISTRIBUTION OF CLINICAL VARIATES

Pre-irradiation assessment	No of patients irradiated with	
	neutrons	photons
Age*		
< 40 years	8	7
40–59 years	9†	9
≥ 60 years	1	0
Sex		
Male	5	8
Female	13†	8
Neurological deficit		
None/minor	10	13
Major	8†	3
Tumour vascularity		
Vascular	5	6
Avascular	13†	10

*Mean age: neutron-irradiated group, 43 years, photon-irradiated group, 43.1 years

†Includes patient subsequently diagnosed as having pituitary adenoma.

TABLE II
DISTRIBUTION OF TUMOURS

Histology	Neutron-irradiated	Photon-irradiated
Astrocytoma		
Grade I	1	0
Grade II/III	7	6
Grade IV	8	6
Astrocytoma + oligodendroglioma	0	3
Oligodendroglioma	1	1
Ependymoma	1*	0
Total	18	16

*Note: patient subsequently diagnosed as having a chromophobe adenoma.

TABLE III

Actuarial survival

Interval at risk (months)	% Patients irradiated with	
	neutrons*	photons
6	52.9	93.8
12	17.6	37.5
24	5 9	12 5
36	5.9	0.0
60	5.9	

*Excluding patient subsequently diagnosed as having a pituitary adenoma.

Treatment at relapse

One patient treated by photons had a subtotal excision of recurrent tumour 18 months after her initial treatment but the tumour recurred and she died 4 months later. Another patient treated by photons had fluid aspirated from a cyst which had reaccumulated at 2 months from therapy. However, he relapsed and died within a short period thereafter

One patient treated by neutrons who had a low-grade malignant astrocytoma was given a short course of CCNU when her tumour was thought to have recurred 30 months from her initial therapy. She has had no further therapy and is alive at 67 months with no evidence of further recurrence but she has a residual moderate neurological deficit.

One other patient treated by neutrons had a course of fortnightly injections of methotrexate following the development of metastatic scalp nodules from a malignant astrocytoma arising in the left parietal region. There was an initial response to chemotherapy but eventually the patient died with widespread extracranial metastatic disease.

The remaining patients had no specific therapy at relapse apart from oral dexamethasone which was given to relieve symptoms and signs of increased intracranial pressure.

Survival

Survival is measured from the date of start of radiotherapy. One patient remains alive 67 months from initial (neutron) therapy. The median survival of the neutron-treated group was 7 months (range 0–67 months) and of the photon-treated group, 11 months (range 3–30 months).

The actuarial survival rates for the two groups are given in Table III. The log-rank test shows that the survival of the neutron-treated patients was significantly poorer than that of those treated by photons over the first 12 months ($\chi^2 = 3.97$, $p < 0.05$) but overall there was no statistically significant difference between the two groups ($\chi^2 = 2.21$, $p > 0.10$).

Cause of death

Two patients treated by photons and one treated by neutrons died following a pulmonary embolus. The patients treated by photons both had clinical evidence of residual tumour but no autopsy was carried out The patient treated by neutrons had an autopsy at which only necrotic remnants of the primary tumour were found.

The remaining patients all had clinical evidence of recurrent and progressive tumour growth before death.

Two patients developed extracranial metastases. One patient with an oligodendroglioma of the right temporal region died 3 months after neutron therapy, having developed paraplegia secondary to an intradural tumour deposit in the lumbar region of the spinal cord.

The second patient, previously referred to, developed widespread metastases which appeared first as skin and subcutaneous nodules around the site of the burr hole. At post-mortem examination the disease was also found to involve the spinal cord, ovary, liver, bone and lymphatics.

Autopsy information

Autopsy was performed on nine of the 18 patients who received neutron therapy. In the group treated by photons autopsy was carried out on seven of the 16 patients.

Residual tumour was identified in all except one of the patients who received neutron therapy. This patient died after 9 months from a massive pulmonary embolism. At autopsy there was evidence of recent severe necrosis at the tumour site but no viable tumour cells could be identified.

Three patients showed evidence at post-mortem examination of intracranial infection Two patients had leptomeningitis, one also having a small cerebral abscess. A third patient had evidence of infection only within necrotic tumour.

Definite abnormal changes in the white matter of the brain, including focal necrosis and demyelination in areas remote from the tumour site, were identified in three patients treated by neutrons. A fourth patient treated by neutrons had less obvious abnormalities in the white matter. These included myelin pallor and the presence of abnormal glial cells which were also considered to be due to the effects of irradiation. In all four patients there was evidence of residual tumour in the brain.

DISCUSSION

This small study compared neutron therapy with megavoltage X-ray therapy for patients with supratentorial gliomas. The dose of neutrons employed was lower than that previously delivered in the treatment of cerebral tumours because of earlier reports of brain damage due to neutron irradiation (Parker et al, 1976a,b; Catterall et al, 1980). This experience with neutron therapy has demonstrated that all but one of the patients had residual tumour at death and that in four of the nine patients on whom autopsy was performed there was evidence of radiation-induced brain damage. It was for these reasons that the trial was closed prematurely. The number of patients recruited was much smaller than originally planned. The experience reported here indicates that a dose of 12.6 Gy fails to produce complete regression of tumour in most patients. Since this trial was completed it has been estimated that the tolerance dose of 16(d + Be) neutrons for brain is about 8.0 Gy fractionated over 4 weeks (Hornsey et al, 1981). Thus, neutron irradiation alone cannot contribute to the more effective management of tumours involving the central nervous system

Acknowledgments

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Book reviews

Small Cell Lung Cancer. Recent Results in Cancer Research Ed. by S. Seeber, pp. 166, 1985 (Springer-Verlag, Heidelberg), DM 108.
ISBN 0-387-13798-X

The incidence of carcinoma of the bronchus has now reached epidemic proportions in many Western countries. While the mortality rate for males with this disease has shown a small decline in recent years, this has been balanced by a steady increase in women such that, in the USA at least, lung cancer now ranks alongside breast cancer as the leading cause of death from malignant disease. More recently, much interest has been aroused following observations that the small-cell histological subtype of lung cancer may respond well to combination cytotoxic chemotherapy and that this response may be reflected in prolongation of median survival times This volume of "Recent Results in Cancer Research" concerns itself exclusively with small-cell lung cancer and it contains standard chapters on diagnosis and the place of surgery, radiotherapy and chemotherapy in current management. The appalling survival prospects with this disease, however, reflect the inadequacy of conventional treatment and this book devotes several chapters to reviews of the basic biology of small-cell lung cancer, wherein may lie the key to future therapeutic advances. Small-cell lung cancers are heterogeneous tumours with the implication that they contain cell populations which might be expected to have differing sensitivities to the individual cytotoxic drugs presently available. This suggests the need for non-cross-resistant drug combinations or the use of more intensive chemotherapy regimes (with or without bone marrow transplantation) if any impact is to be made. While there has been a depressing lack of benefit from these approaches to date, this does not disqualify them but rather stimulates the need to search for newer and more effective systemic therapies

Apart from a few typographical errors, this book is well produced and, despite the recent proliferation of textbooks on lung cancer, this relatively small volume (166 pages) represents an informed and up-to-date review of the subject and is to be recommended to those who wish to keep abreast with developments in both diagnosis and management.

D. TIMOTHY

Lung Cancer. Diagnostic Procedures and Therapeutic Management With Special Reference to Radiotherapy. Ed by Charles W. Scarantino, pp. xi+173, 1985 (Springer-Verlag, Heidelberg), DM 120.
ISBN 3-540-13176-0

This multiauthor book attempts to cover the general topic of lung cancer, but with special reference to radiotherapy Numerous books on lung cancer have been published recently. Most have addressed themselves to specific aspects and not attempted to be this comprehensive. The present book does suffer from not quite achieving that worthwhile, but difficult, aim Individual chapters have many excellent aspects covering general approaches to the patient, anatomical and pathological considerations, diagnostic workup, the role of radiotherapy and results A good chapter on experimental tumour biology is, however, misplaced in a book of this type. Sadly, its relevance to lung cancer is barely justified. A further criticism is the general layout of chapters which makes it difficult to separate very real differences in the problems associated with small-cell and non-small-cell carcinoma However, there are many good aspects of the book, including comprehensive bibliographies available for further reference. It is unlikely to be of value to the specialist in lung cancer but should provide well worthwhile reading to those with a more general interest in the problem

N. M. BLEEHEN

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The results of a randomised trial of mixed-schedule (neutron/photon) irradiation in the treatment of supratentorial Grade III and Grade IV astrocytoma

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ABSTRACT

A randomised trial is reported of mixed-schedule (neutron/photon) irradiation compared with photon therapy for patients with Grade III or Grade IV astrocytoma. Thirty-one patients were allocated to be treated by the neutron/photon regime and 30 patients by photons. The median survival was 4 months in the mixed-schedule group and 8 months in the photon group. The survival rates were not significantly different. All patients who died had evidence of residual brain tumour. None had signs of radiation-related morbidity.

The treatment of high-grade astrocytomas in adults continues to present a challenge. The prognosis is very poor for almost all patients who present with these tumours. Fast-neutron therapy has been used alone in the hope of improving results but without success. It is now recognised that the central nervous system is particularly sensitive to neutron irradiation. Severe demyelination, gliosis and vascular damage have been reported after doses that failed to eradicate the primary tumour (Shaw et al, 1978; Catterall & Bewley, 1979; Duncan et al, 1986).

It has been suggested that the combination of neutrons and photons may be advantageous (Nelson et al, 1975; Rasey et al, 1977). Mixed-schedule treatments have usually been given using two fractions of neutrons alternating with three fractions of photons each week. Laramore et al (1978) first reported a series of patients managed in this way who showed no improvement in survival. An increase in the neutron contribution to the total dose could not be advised since a higher incidence of brain necrosis would be expected. We felt that it would be worthwhile evaluating the mixed-schedule approach using a smaller contribution of neutron irradiation. This paper presents the results of a randomised trial of mixed-modality treatment compared with photon therapy alone.

PATIENT SELECTION AND RANDOMISATION

All patients had histologically confirmed supratentorial astrocytomas, Grade III or IV. Patients were 16 years of age or older and were considered fit for a radical course of radiotherapy over 4 weeks. Informed consent was obtained from all patients. Following confirmation of eligibility for inclusion in the trial, patients were stratified by age (16–39 years, 40–59 years, 60 years and over) and by neurological status (minor or major neurological disability due to their brain tumour) before randomisation. Minor neurological disabilities corresponded to Grades 1 and 2 of the Medical Research Council definition of neurological status (MRC Working Party, 1983) and major deficits to Grades 3 and 4 (Table I). Treatment allocation was obtained by opening a sequentially numbered sealed envelope containing the randomly generated treatment option.

RADIOTHERAPY

All patients were treated with the aid of a beam-direction shell to ensure the accuracy of treatment. Parallel opposed lateral fields (normally 11 cm × 16 cm) were used to treat the whole brain and were aligned using front and back pointers located on the shell for both neutron and photon treatments.

The photon therapy was given by a 4 MV linear accelerator. A target absorbed dose of 47.5 Gy was delivered in 20 fractions over 4 weeks.

TABLE I

MRC ASSESSMENT OF NEUROLOGICAL STATUS

1 No neurological deficit
2 Some neurological deficit but function adequate for useful work
3 Neurological deficit causing moderate functional impairment, *e.g.* able to move limb/s only with difficulty, moderate dysphasia, moderate paresis, some visual disturbance (*e.g.* field defect)
4 Neurological deficit causing major functional impairment, *e.g.* inability to use limb(s), speech or visual disturbances
5 No useful function, inability to make conscious responses

The RBE for normal brain of the d(15)+Be neutron beam, at photon dose fractions of 2.38 Gy, was estimated to be approximately 4.0 (Hornsey et al, 1981; Halnan & Hornsey, 1981). The mixed schedule chosen, therefore, comprised eight fractions of 0.6 Gy of neutrons on Tuesdays and Thursdays and 12 4 MV photon fractions of 2.375 Gy on Mondays, Wednesdays and Fridays over 4 weeks. The total target absorbed dose from the neutron treatment was 5.1 Gy (7.8% gamma) and the target absorbed photon dose was 28.5 Gy.

Dexamethasone was administered in the perioperative period in the majority of cases and thereafter as required.

Two patients developed a wound infection post-operatively but only in one, where the bone flap became infected, was reoperation necessary. Apart from this latter patient, all patients started their course of radiotherapy within 1 month of operation.

RESULTS

A total of 61 patients was entered into the study between November 1979 and December 1982. Thirty-one patients were allocated to be treated by the mixed schedule and 30 patients by photon therapy. The distribution of patients by age, sex and neurological deficit is given in Table II and is clearly similar in the two groups. Table III gives the distribution of surgical procedures and histological grade and shows that more patients in the mixed-schedule group had a craniotomy and attempted excision of the glioma than in the group treated by photons. The difference is not significantly different. In each group there were four patients with cystic tumours. In the mixed-schedule group, four patients had tumours that were noted to have less aggressive features, one showing features of an oligodendroglioma. There was considerable interdependence of many of these variates in that the younger patients, under 40 years of age, had less aggressive gliomas histologically and less serious neurological complications.

TABLE II

DISTRIBUTION OF PATIENT CHARACTERISTICS

	No. of patients irradiated with	
	mixed-schedule irradiation	photons
Patients randomised	31	30
Age		
< 40 years	3	2
40–59 years	16	15
≥ 60 years	12	13
Sex		
Male	20	21
Female	11	9
Neurological disability		
None	4	3
Minor	15	13
Major	12	14

TABLE III

DISTRIBUTION BY SURGERY AND HISTOLOGICAL GRADE

	No. of patients irradiated with	
	mixed-schedule irradiation	photons
Surgical intervention		
Burr-hole biopsy	11	6
Craniotomy and biopsy	7	16
Craniotomy and excision	13	8
Histological grade		
Astrocytoma Grade III	22	21
Grade IV	9	9

Three patients in the mixed-schedule group and one in the photon group did not complete radiotherapy because of rapid deterioration in their condition secondary to tumour extension. Three died within 1 month of starting treatment and the other, who was in the mixed-schedule group, died 5 weeks after starting treatment.

Patients treated by photons developed mild scalp reactions but the mixed-schedule patients generally developed a bright or dusky erythema of the scalp, especially around the ears. One patient in the mixed-schedule group developed patchy, moist desquamation. His treatment, therefore, omitted one fraction each of neutrons and photons.

All patients developed epilation. In the mixed-schedule group it was permanent apart from a little fine, patchy regrowth over the scalp. The patients treated by photons showed eventual good regrowth of hair, although it tended to be finer than before.

A few patients reported mild nausea during radiotherapy but this was not a serious problem.

Further therapy on relapse

The majority of patients received no further specific management for tumour progression. Dexamethasone was used as symptomatic medication as required.

One patient in the mixed-schedule group was started on a course of vincristine and CCNU 24 months after radiotherapy. He showed no improvement and died 2 months later.

One of the patients treated by photons had macroscopic excision of recurrent tumour 12 months after radiotherapy but died 10 months later with further regrowth of tumour.

One patient with a cystic tumour was noted to have reaccumulation of fluid 2 months after mixed-schedule

TABLE IV

ACTUARIAL SURVIVAL

Survival (months)	% of patients irradiated with	
	mixed-schedule irradiation	photons
6	38.7	60.0
12	22.6	20.0
24	19.4	6.7
36	12.9	6.7

radiotherapy and a Rickham's reservoir was inserted. It worked satisfactorily but the patient died 23 months later with evidence of solid tumour recurrence.

Survival

All patients were treated at least 2 years ago. Of the six patients who are still alive, four were treated by mixed-schedule therapy and two by photon therapy. The median survival is 4 months (range 0–60 months) for the mixed-schedule group and 8 months (range 0–48 months) for the group treated by photons.

Table IV shows the survival rates for the two groups. There is no statistically significant difference in survival (log-rank test: $\chi^2 = 0.084$, $p > 0.7$).

Cause of death

Primary brain tumour. All patients who died had clinical and/or radiological (CT scan) evidence of local progression of the tumour.

Only four patients in the mixed-schedule group and one patient treated by photons had an autopsy. All showed persistent tumour to be present. None showed any evidence of demyelination or abnormal gliosis. No patient developed the syndrome of progressive dementia associated with radiation-induced damage or any other features which could not be explained by regrowth of the primary brain tumour.

In the mixed-schedule group one patient, who died 4 months after radiotherapy, was found to have abscesses in the brain and lungs as well as persisting tumour. Another committed suicide 14 months after treatment. Clinically and radiologically he had shown a good response to treatment but at autopsy residual tumour was identified in the brain.

Complications of corticosteroid therapy. In the group treated by photons there were three patients in whom the immediate cause of death may have been related to the long-term administration of corticosteroids. One patient had a pulmonary embolism, one patient was reported to have had a severe terminal haemorrhagic diathesis and the third patient had symptoms of perforation of an abdominal viscus before death. However, all three had evidence of residual tumour in the brain.

DISCUSSION

This study has evaluated a course of mixed neutron and photon irradiation, the absorbed dose of which did not exceed the tolerance of normal brain. There was no clinical evidence of progressive radiation-induced brain damage and, in the five patients on whom autopsy was performed, no histological evidence of demyelinisation, abnormal gliosis or vascular damage was found. Unfortunately, there was no evidence that the local control of the primary tumour was any better following the neutron/photon regime than after photon therapy alone. Survival was similar in the two groups as were the causes of death. When account is taken of the experience of other investigators (Table V) it would seem that it is unlikely that mixed schedules of neutrons and photons will contribute to any improvement in the prognosis of patients with cerebral gliomas.

If neutron therapy is to be explored further it should be as a boost localised to the site of the primary tumour. Such a technique would minimise the risk of producing neutron-induced damage to the brain remote from the tumour while concentrating the neutron radiation on the residual tumour site, which may be defined by computed tomography. Three studies have been reported in which a boost of neutron irradiation was given to the primary tumour site after a course of photon therapy to the whole brain, or to a large volume of brain. Battermann (1980) delivered an absorbed photon dose of 30.6 Gy in 17 fractions over 23 days to the whole brain followed by a neutron boost of 11.2 Gy in 16 fractions over 22 days. Survival of a group of 18 patients with Grade III or IV astrocytomas was considered to be similar to that which might be expected after megavoltage X-ray therapy. Griffin et al (1983) have reported the results of a clinical trial (RTOG 76-11) in which patients were given 50.0 Gy in 25 fractions over 5 weeks to the whole brain and were subsequently randomised to receive a neutron or photon boost to the primary site: 81 patients received a neutron boost and 79 a photon boost, giving a dose of 15.0 Gy in six to 10 daily fractions or its equivalent with the various neutron beams. Again, no significant difference in survival was observed in the two groups. It was, however, claimed that patients who received the "neutron boost" were dying without evidence of tumour progression compared with the "photon boost" group, most of whom had progressive local tumour. Breteau et al (1984) treated patients with Grade IV astrocytoma using a course of irradiation concentrated in time. The whole brain, or a large volume of it, was irradiated by megavoltage X rays to a dose of 18.0 Gy in three fractions over 3 days. After 3–4 weeks, a course of d(50)+Be neutron irradiation was given to the primary tumour site, 6.0 Gy in three fractions in 3 days. The average survival of these patients was 7 months, similar to that reported in other series and was comparable with an historical control group of patients treated by concentrated irradiation with photons only. It would seem desirable that these neutron boost

TABLE V

REPORTED SURVIVAL RATES OF PATIENTS WITH GLIOMAS TREATED BY NEUTRON IRRADIATION

Tumour and grade	Treatment	No of patients	Survival at 12 months (%)	Survival (range), months	Reference
(A) Randomised trials					
Astrocytoma III, IV	Neutrons alone	30	30	10.0 (3–22)	Catterall et al, 1980
	Photons alone	33	36	11.4 (1.5–38) (mean)	
Astrocytoma IV	Photons + neutron boost	81	40	9.8	Griffin et al, 1983
	Photons + photon boost	79	40	8.7 (median)	
Astrocytoma II, III, IV	Neutrons alone	18	18	7 (0–67)	Duncan et al, 1986
	Photons alone	16	37	11 (3–30) (median)	
Astrocytoma III, IV	Neutrons/photons	31	23	4 (0–60)	Duncan et al (this series)
	Photons alone	30	20	8 (0–48) (median)	
(B) Non-randomised trials					
Astrocytoma III, IV	Photons + neutron boost	22	32	6.0 (1–16) (mean)	Battermann, 1980
Astrocytoma III, IV	Neutrons alone	26	22	9.4 (0.5–39)	Laramore et al, 1978
	Neutrons/photons	10	20	7.6 (0.5–19)	
	Photons + neutron boost	1	Alive and well	(mean)	
Astrocytoma IV	Photons + neutron boost	18	24	7.0 (1–12) (mean)	Breteau et al, 1984
Astrocytoma III, IV	Neutrons alone	21	23	7.2 (mean)	Parker et al, 1976

schedules should be further evaluated by controlled trials. However, the evidence so far available would suggest that the tolerance dose of neutrons for normal brain may be lower than the dose required to give a significant probability of tumour control.

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We acknowledge our indebtedness to the Medical Research Council, the Cancer Research Campaign and the Lothian Health Board for providing the Cyclotron Unit in Edinburgh and for support of its operation and the clinical trial programme. We would thank the engineering and technical staff of the cyclotron for ensuring its reliable performance and to the physicists for their professional support in controlling the accuracy of the techniques, dosimetry and treatment planning. We are grateful to the staff of the Department of Neurosurgery and the Neuropathology Laboratory, particularly the late Dr A. F. J. Maloney, at the Western General Hospital, Edinburgh for their co-operation, advice and encouragement and to Mrs Irene Noble for her assistance in preparing this manuscript.

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Book review

Gynaecologic Cancer. By Arlene A. Forastiere, pp. viii + 307, 1984 (Churchill Livingstone, New York), £36.00
ISBN 0–443–08274–X

This is very much an American book. It talks of radium used for intracavitary therapy and doses measured in mg h, and afterloading techniques are dismissed in a few lines in the past tense. It is nonetheless stimulating and well written, with a wealth of references, albeit predominantly to authors in the USA. The editor wisely did not plan to cover all topics, but concentrated on the main areas of controversy and interest.

I particulary liked the chapter on chemotherapy for carcinoma of the cervix, which includes chemotherapy given before radiotherapy for advanced disease. It is clear that this is a potentially valuable technique, but it requires further investigation into the interaction of radiotherapy and chemotherapy, and optimum timing of the two modalities in relation to late (rather than early) morbidity and tumour control.

Ovarian carcinoma is well covered, but with scant enthusiasm for the benefits of radiotherapy and a persistent conviction that second-look laparotomy is an important part of general management. Again, in the section on endometrial carcinoma, the author (a gynaecologist) takes a very pessimistic view of the value of post-operative radiotherapy in early but poor risk cases (poorly differentiated tumours with deep myometrial invasion or involvement of the cervix). His concern as to whether the high risk of late radiation morbidity is justified would not be echoed by many British oncologists.

The epidemiology of both cervical and endometrial carcinoma is very well covered and the chapter on carcinogenesis following alkylating agents and radiation therapy is novel and has some useful references.

In general, the book will be of particular interest to oncologists experienced in managing gynaecological malignancy because of the detailed and well referenced discussion on controversies. However, those who are new to the subject may, despite the excellent summaries, be confused. It is a useful book to have in the library.

THELMA D. BATES

Note. This review was originally published in the January 1986 issue of the Journal (p. 52) but contained several errors. We have printed the corrected version above, with apologies to the author and reviewer.

Book reviews

Liver Cancer Ed by Joseph C. Bottino, Richard W. Opfell and Franco M. Muggia, pp. xvi+391, 1985 (Martinus Nijhoff, Boston), £67.95/$82.50.
ISBN 0-89838-713-2

This is a 391-page text from the USA, meant to cover therapeutic approaches to liver and biliary tract cancer as a "comprehensive, yet practical, overview". There are 40 authors of 23 chapters, all American except for Falkson and Coetzer from Pretoria, South Africa, and including some of the most distinguished surgical, medical and radiation oncologists from the Mayo Clinic, the NIH, Yale, Houston, New York, Roswell Park, Los Angeles, Ann Arbor and Detroit.

There are good descriptions of pathology, imaging, surgery, chemotherapy, radiation therapy and combinations of these. Hepatic artery ligation, embolisation, intra-arterial therapy, pumps and catheters, and even thermochemotherapy (by Ramming and Storm) are described in some detail. Most chapters are reasonably up to date for the end of 1983, with a few 1984–85 references, usually work in course of publication. The chapter on diagnostic radiology comes from Lewis and Wallace at the MD Anderson Hospital and that on nuclear medicine from Froelich, Thrall and Swanson at the Henry Ford Hospital. Radiation therapy is well described by Leibel from San Francisco.

There are two important gaps. The substantial work now going on to develop vaccines against hepatitis viruses is scarcely mentioned, probably on purpose because it will not be freely available for some time yet. The use of the newer monoclonal antibodies is similarly omitted, presumably since their value is by no means proven, though the uses of ferritin and CEA antibodies are covered. Treatment by somatostatin is just squeezed into Moertel's very good chapter on the carcinoid syndrome, but medical treatment of metastases from other apudomas and hormonal tumours is also not covered.

The book is a good interim account of an attempt to deal with these important tumours that, unfortunately, are still so difficult to treat well.

Keith E Halnan

Ovarian Cancer Ed. by C. N. Hudson, pp. x+373, 1985 (Oxford University Press), £35.00.
ISBN 0-19-261367-7

This is an excellent textbook which covers clearly and comprehensively the complexities of diagnosis, staging and management of a "silent" tumour which is responsible for more deaths than carcinoma of the cervix and body of uterus together. It is up to date and well referenced. It is easy to read, uses italics in a subtle way to stress important points and generally has an air of optimism in the way that recent advances are given emphasis. Rare tumours, as well as the epithelial carcinomas, are included.

Whilst the fundamental importance of optimum initial surgery is stressed, useful guidelines are given for the few cases where conservative surgery can be considered. There is a thoroughly balanced approach to the many unanswered questions concerning adjuvant radiotherapy and chemotherapy in early carcinoma and the desirability of second-look laparoscopy in the late cases.

Of particular note to those with a deeper interest are the chapters on epidemiology, cytogenetic analysis as a possible aid to diagnosis and prognosis, and monoclonal antibodies as the hoped-for breakthrough in diagnosis and therapy.

In my opinion, the only area in which this textbook is not completely up to date is the short section on terminal care. Pain, nausea and vomiting of unrelieved intestinal obstruction no longer necessitate intravenous drugs to the point of clouding of consciousness. Hopefully, in a second edition this section can be changed.

Without doubt, surgeons and oncologists who have patients with ovarian cancer will want this book in their library.

Thelma D. Bates

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Radioiodine treatment of solitary functioning thyroid nodules

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ABSTRACT

Forty-eight patients with hyperthyroidism due to a single toxic nodule have been treated with radioiodine (^{131}I). The mean follow-up period is 37 months. All patients were rendered euthyroid and no cases of hypothyroidism have been observed. Forty patients required only one dose of ^{131}I to render them euthyroid, six patients required more than one dose and two patients initially rendered euthyroid relapsed during follow-up and required further ^{131}I treatment. It is concluded that a single fixed dose of ^{131}I is a simple, effective treatment for a solitary toxic thyroid nodule and does not cause hypothyroidism.

Radioiodine (^{131}I) is generally regarded as a suitable treatment for patients with hyperthyroidism due to single or multiple hyperfunctioning nodules (Plummer's disease) (Becker & Hurley, 1982). We have previously reported successful control of hyperthyroidism using a simplified regime of a single 500 MBq (15 mCi) dose of ^{131}I in patients with either single or multiple hyperfunctioning nodules (Ng Tang Fui & Maisey, 1979). Because there is suppression of the normal perinodular thyroid tissue, which thus receives a low radiation dose from ^{131}I, the incidence of hypothyroidism developing later is usually low (Hamburger, 1975). Our early findings confirmed this and it has also been supported by the findings of Ross et al (1984). However, Goldstein and Hart (1983) reported an incidence of hypothyroidism of 36% following ^{131}I therapy, which is similar to that following the treatment of toxic diffuse goitre (Graves' disease). The purpose of the present study was to review the results of our longer follow-up and more extensive experience of patients with a solitary hyperfunctioning nodule treated with a single-dose regime of ^{131}I.

MATERIALS AND METHODS

We have reviewed 49 consecutive patients with thyrotoxicosis due to a solitary hyperfunctioning nodule who were referred to the thyroid clinic at Guy's Hospital and who were treated with ^{131}I. One of these patients has gone abroad and information is not available; otherwise the follow-up is complete.

The mean age is 59 (range 31–85) years with a female to male ratio of 5.4 : 1. All the patients were clinically and biochemically hyperthyroid by the standard criteria. This included a serum total triiodothyronine (T3 normal range 1.2–3 nmol/l) and serum total thyroxine (T4 normal range 50–150 nmol/l) measured by radioimmunoassay. A standard TRH stimulation test was performed when necessary.

A radionuclide thyroid scan was performed in all patients: 180 MBq of technetium 99m as pertechnetate was injected intravenously and imaging was performed with a gamma camera fitted with a pinhole or a specially designed long, parallel-hole collimator. Imaging was started 20 min after injection and 100 000 counts were recorded.

Radioiodine treatment consisted of a single oral dose of 550 MBq (15 mCi) of ^{131}I with the exception of three patients who were given 370 MBq (10 mCi). When antithyroid drugs had been prescribed before referral they were always discontinued, usually for several weeks and always for at least 3 days before treatment, and a scan was again performed prior to ^{131}I administration to confirm complete suppression of extranodular thyroid tissue. When clinically indicated, hyperthyroid symptoms were controlled with propanolol 40 mg every 8 h for 2–8 weeks following the ^{131}I administration.

The thyroid scan and thyroid function tests were repeated 6 months after ^{131}I treatment. Subsequent follow-up continued at 6-monthly or annual intervals with further scans performed as clinically indicated. On initial clinical examination no nodule was palpable in six cases, 10 had a uniformly nodular gland and in the remainder there was a clear-cut nodule with the remainder of the gland either normal or slightly nodular. All cases had a single hyperfunctioning nodule, with suppression of the remainder of the gland demonstrated on the scan.

RESULTS

Six months after the radioactive treatment, 41 of the 48 patients were clinically and biochemically euthyroid with normal T3 and T4 levels and the TRH test showed a normal response. The scan showed complete or partial resolution of the hyperfunctioning nodule with recovery of uptake by previously suppressed thyroid tissue.

The remaining seven of the 48 patients remained hyperthyroid at 6 months, with persistence of the

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hyperfunctioning nodule and suppression of normal thyroid tissue on the scan. Six of these seven patients were treated again with 550 MBq of ^{131}I; four became euthyroid with a normal TRH response after 6 months; two required a third dose of ^{131}I and were euthyroid 6 months later. One patient who was hyperthyroid at 6 months after the initial ^{131}I therapy was found to have a disseminated malignancy from carcinoma of the bronchus. Further therapy was delayed and he subsequently became euthyroid. The 48 patients have now been followed up for a mean period of 3.1 (range (2–10) years. Two patients who were euthyroid 6 months after the first dose of ^{131}I subsequently relapsed 12 months and 18 months later, respectively; both had incomplete functional resolution of the nodule on follow-up scans and both patients were euthyroid 6 months after a second dose of ^{131}I with complete resolution of the functional activity in the nodule on the scan.

During the follow-up period no patient has become permanently hypothyroid. One patient had transient mild biochemical hypothyroidism with a TSH level of 11 but 5 years later remains euthyroid with a normal TSH. Five patients have died during the follow-up period. None of the deaths has been related to hyperthyroidism and no patient had evidence of hypothyroidism.

Discussion

We have now followed up 48 hyperthyroid patients with single hyperfunctioning nodules. They were all treated with ^{131}I and none have developed clinical or biochemical hypothyroidism. These findings confirm our previous report (Ng Tang Fui & Maisey, 1979), support those of Ross et al (1984) and conflict with the findings of Goldstein & Hart (1983). The main differences lie in the frequency of thyrotoxicosis. All the patients in our study group and those of Ross et al (1984) were clinically and biochemically hyperthyroid, whereas a significant proportion (70%) of those in the series of Goldstein and Hart (1983) were euthyroid at the time of ^{131}I administration. Hyperthyroidism results in TSH suppression and, hence, suppression of the uptake of radioiodine tracers into normal thyroid tissue. Because the radiation dose from ^{131}I is predominantly from β particles, which have a very short range in tissue, and not from the high-energy gamma photons, the radiation dose to suppressed tissue will be very small and, therefore, subsequent hypothyroidism is unlikely If, on the other hand, there is incomplete suppression, as in a euthyroid patient with an autonomous functioning nodule, the normal tissue uptake of the therapeutic ^{131}I will result in a significant radiation dose and, consequently, a predictably higher incidence of hypothyroidism as found by Goldstein & Hart (1983). The clinical implications of these findings are that ^{131}I is a reliable treatment for hyperthyroidism associated with a single hyperfunctioning nodule and long-term follow-up to detect hypothyroidism may not be necessary for this group of patients. If ^{131}I treatment of a hyperfunctioning nodule in a euthyroid patient is clinically indicated, for example, when associated with atrial fibrillation, then a high incidence of hypothyroidism should be anticipated. This may include patients who have been rendered euthyroid by antithyroid drugs if the drug treatment cannot be discontinued for a period long enough to allow complete resuppression of the normal thyroid tissue.

Eight patients required more than one dose of ^{131}I to provide long-term control of hyperthyroidism. All of these patients either remained hyperthyroid or showed incomplete destruction of functional activity of the nodule after the initial ^{131}I treatment. This finding suggests that a larger initial dose of ^{131}I may be necessary in some patients, based on a more detailed calculation of predicted radiation dose derived from nodule volume, uptake and turnover rate. It has been calculated (Gorman & Robertson, 1978) that the radiation dose from 550 MBq received by a 3 cm nodule would be 246 Gy and, for the same dose, a 5 cm nodule receives 56 Gy. These calculations assume a fixed 30% uptake and a 5-day effective half-life, both of which significantly alter the radiation dose received by the nodule. Nevertheless, six out of 45 patients in the series of Ross et al (1984) required more than one dose of ^{131}I, in spite of dosimetric calculations, which is not significantly different from our rate. Thyroid tissue sensitivity to radiation remains an unknown factor and a prospective clinical trial would be necessary to confirm this. The clinical significance of these findings is that it is probably necessary to follow up patients who have persistent functional activity in the nodule following ^{131}I ablation, especially if the TRH test remains unresponsive.

This study has shown that a simple approach to the treatment of hyperthyroidism due to a single functioning thyroid nodule is effective. A single dose of 550 MBq requires the minimum investment of time and resources and will cure the majority of patients with no long-term incidence of hypothyroidism. It also shows the importance of early diagnosis by radionuclide thyroid scanning because in only 33 of these 48 cases was it possible to make the diagnosis clinically by palpating a single thyroid nodule Without a thyroid scan, 16 may not have been diagnosed as having a solitary nodule and may, therefore, not have received optimal management. All patients with hyperthyroidism who have a solitary palpable thyroid nodule, a multinodular gland or no easily palpable thyroid should have a radionuclide scan to identify a solitary hyperfunctioning thyroid nodule.

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Book reviews

CT Densitometry in Osteoporosis. By L E. H. Lampmann, S A. Duursma and J. H. J. Ruys, pp. 124, 1984 (Martinus Nijhoff Publishers, The Hague), £24.25.
ISBN 0–89838–633–0

Until the introduction of CT bone densitometry no satisfactory method was available for the separate *in-vivo* estimation of vertebral trabecular bone mass. The development of this technique, largely pioneered by Genant and his co-workers in San Francisco, has been one of the major advances in the clinical investigation of metabolic bone disease. The authors of this monograph describe their experience of this technique in a series of 106 patients who were studied in detail in the University Hospital of Utrecht in Holland.

After a brief account of bone physiology the authors review the currently available techniques for the estimation of bone mass (radiogrammetry, photon absorptiometry and CT). The basic principles of CT, including radiation dose, are outlined briefly and the possible sources of error of CT densitometry (beam hardening, partial volume effect) are discussed The precision and accuracy of the technique have been determined by phantom studies. In the clinical studies vertebral trabecular bone mass was expressed in terms of CT attenuation or equivalents of calcium hydroxyapatite, and the findings of a close correlation between the composition of adjacent vertebrae and a fracture threshold of 80 HU are in good agreement with other published observations.

The sections of the book dealing with CT are satisfactory; other sections are somewhat superficial The chapter dealing with comparative methods of bone densitometry is more a series of abstracted notes than a coherent synthesis of the literature they cite, but it does provide many useful references. There are numerous typographical errors throughout the text.

I am not quite certain to whom this book is directed Perhaps it would be of most value as a basis for radiologists contemplating CT bone densitometry, although more comprehensive accounts of the technique now appear in several of the recent standard radiological texts.

J. E ADAMS

Clinical Arthrography, 2nd edit. By Rolf-D. Arndt, John W Horne, Richard H. Gold and Donald D Blaschke, pp. xiii + 275, 1985 (Williams & Wilkins, Baltimore), £58.00
ISBN 0–683–00256–2

This is the second edition of a comprehensive monograph dealing with arthrography, not only of the knee but of all the major peripheral joints and also the temporomandibular joint The largest section is on the knee Both single- and double-contrast techniques are described in detail. The author recommends a rigid suction-cap restraining device for the knee, which I find clumsy and cumbersome.

Their classification of meniscal tears is not accompanied by local line diagrams, which would have aided comprehension Indeed, a lack of line diagrams is evident throughout this volume

The section on hip arthrography in infants is rather sketchy while, in the adult, the large section on loose or infected hip replacements does not mention isotope scanning which, though not arthrographic, surely cannot be ignored in this context. I found the section on arthritides helpful.

The wrist is not commonly examined by arthrography but this section was of benefit to me. The chapter on temporomandibular-joint arthrography was concise and the radiographs were accompanied by line diagrams which made the chapter more easily understood.

Illustrations are plentiful and generally of good quality References are not numbered in the text, but listed alphabetically after each chapter.

Reading about techniques does not, of course, match practical experience, but this book can be read with profit by the trainee, as much information is to be found in its 275 pages.

P. RENTON

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The radiosensitivity of microcolony- and macrocolony-forming cells in mouse tail epidermis

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ABSTRACT

A new microcolony technique is described for measuring the survival of colony-forming cells in mouse tail epidermis. The survival curve is characterised by $D_0 = 2.70 \pm 0.12$ Gy. The number of microcolonies per cm^2 is similar to the number of macrocolonies after high doses, which shows for the first time that all microcolonies ($\geqslant 32$ cells) in epidermis develop into macrocolonies. At low doses the number of macrocolonies underestimates the number of colony-forming cells because of coalescence of microcolonies to form macrocolonies. This results in a lower apparent sensitivity of macrocolony-forming cells by a factor of about 1.5. About 3% of basal cells in tail epidermis appear to be capable of colony formation

Residual epidermal injury in various sites in the mouse after irradiation has been widely studied using techniques involving skin reactions, deformity, or necrosis (*e.g.* Brown & Probert, 1973; Denekamp, 1975; Hendry et al, 1977; Hornsey & Field, 1980), and some cellular defects associated with long-term injury have been described using the mouse tail (Hendry et al, 1982). In order to study any changes in radiosensitivity of colony-forming cells associated with residual injury measured in terms of gross skin response, a microcolony technique has now been developed for tail epidermis. This site is preferred to dorsal skin, which is used for most colony studies, because dorsal skin contracts markedly after irradiation (Hayashi & Suit, 1972) whereas tail skin is overlying the bony tail structure and this will limit the shrinkage. This lack makes re-irradiation of the same region of skin technically simpler and the results easier to interpret. Although a macrocolony technique has been described for tail epidermis (Hendry, 1984), the method produces survival data spanning only one decade and hence has poor resolution regarding changes in radiosensitivity. The microcolony technique, producing data over three decades in survival, is described here in detail for mice receiving radiation for the first time. The data are compared with macrocolony data and with data in the literature concerning epidermal microcolonies and macrocolonies.

MATERIALS AND METHODS

Female B6D2F$_1$ mice at an age of 3 months were used throughout. The tail skin was not plucked either before or after the irradiation. The middle 3 cm of tail was irradiated with 300kVp X-rays (HVL = 2.2 mm Cu) at a dose-rate of 2.0 Gy per min, as described previously (Hendry et al, 1976). The tail holes in the jig were kept at 37°C, near body-core temperature. The unanaesthetised mice were confined in perforated perspex tubes and were positioned 5 min before irradiation, to allow the tails to acclimatise to the 37°C temperature which was maintained during irradiation. Between four and 12 mice were used per dose point, with the larger numbers for the higher doses where colony numbers were low. The mice were inspected daily after irradiation and were killed at various times for counting colonies. The time of assay for each mouse was chosen on the basis of specified levels of skin reaction, and the validity of this approach is described below. The reactions used were erythema, severe erythema, and slight dry desquamation, because it was found that discrete colonies, most containing more than 32 cells, were detected at times corresponding to these levels of reaction. The erythema reactions were difficult to discern in the skin of these black mice, and they were detected by close scrutiny under a lamp.

On the day the mice were to be killed, they were injected intraperitoneally with 0.01 mg (per mouse) of the mitotic inhibitor vincristine sulphate, three times at intervals of 3 h. Three injections were given to accumulate more mitoses in order better to identify the growing colonies. They were killed 3 h after the last injection, and then the hairs were removed from the tails using at least eight applications of Sellotape. Whole-mount preparations of the epidermis were made using a modification of a method used by Mitani and Potten (personal communication). The skin was dissected away from the underlying tissues, put in Carnoy's fixative overnight, and then transferred to 70% ethanol The samples were hydrolysed in 5N HCl at room temperature (approx. 22°C) before inspection under a dissection microscope. Fine-point forceps were used to remove, very carefully, all the connective tissue and the hair follicles. Then the epidermal sheet was put on a subbed slide and air-dried. The sample was stained for about 90 min with Schiff's reagent, cleared, and mounted for scoring.

Colonies were identified as foci of high cell density with a mitotic index ranging from about 5% to about 50%, and with a lack of melanin (Fig. 1). Very few

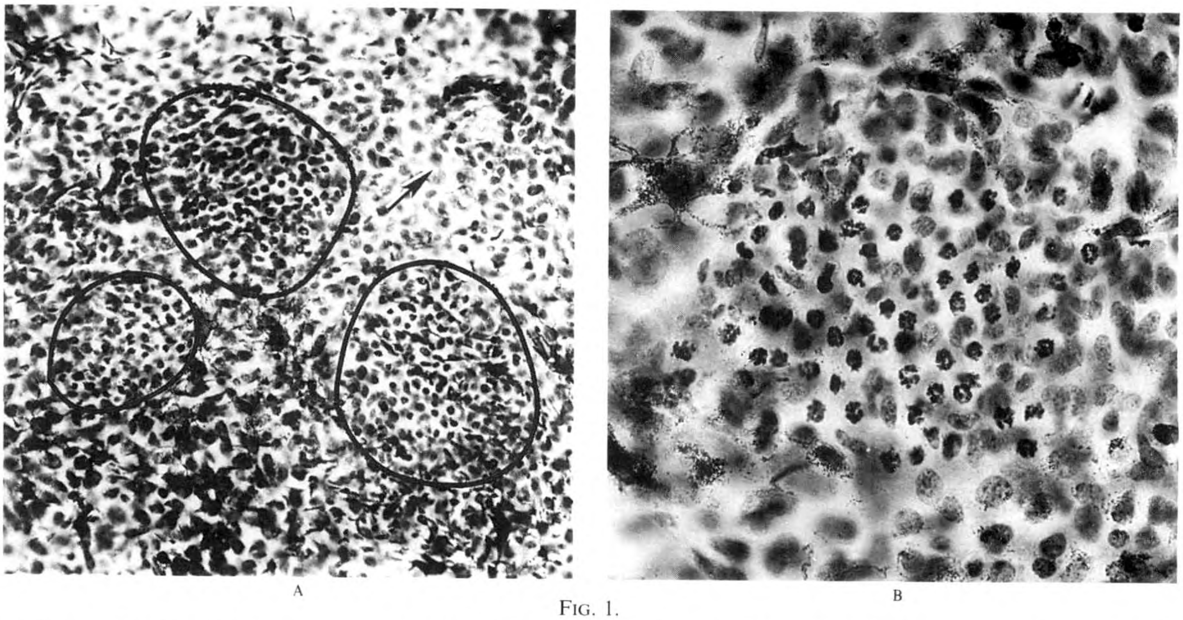

FIG. 1.

(A) Three neighbouring microcolonies at day 15 after 15 Gy. The arrow points to a hair follicle opening. ×60. (B) A single microcolony at day 15 after 17.5 Gy, showing a high proportion of mitotic cells. ×120.

colonies were observed between the squame mounds on the tail, *i.e.* associated with hair follicles. Colony size was estimated initially using cell number and later by colony area (measured using a Kontron-MOP Videoplan), which was proportional to cell number. Colonies were counted in the middle 2 cm of the irradiated 3 cm length of tail to avoid problems of cell migration and dose inhomogeneity at the edges of the irradiated field (Hendry, 1984). For the cell survival data, colonies containing 32 cells or more were counted. Tails were sampled between 10 and 21 days after irradiation, most being sampled between days 13 and 17.

Other mice receiving doses of 30 Gy or more to the tail were left for longer intervals of time until the skin reactions were more severe and when macrocolonies could be counted, as described by Hendry (1984). The macrocolonies were scored between 19 and 28 days after irradiation, and most scoring was performed between days 20 and 23.

A survival curve was fitted to the data points using a multitarget equation including a single-hit term, in the computer programme described by Gilbert (1969). A bending survival curve, described for example by a linear/quadratic equation, could have been used, but there was no clear curvature in the majority of the data in the high dose range, as judged by eye (see Figs 3 and 4). A similar lack of curvature was reported for epidermal colony forming units (CFU) over five decades of depopulation by Withers (1976b).

RESULTS

The assay time for microcolonies for 80% of the mice was between 13 and 17 days after irradiation (Table I).

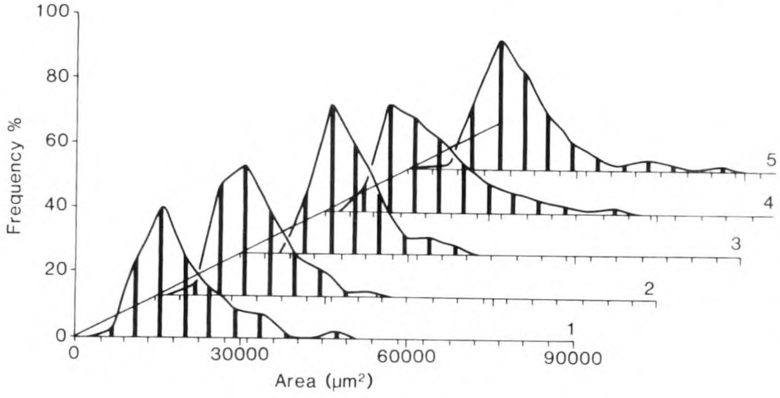

FIG. 2.

Clone-size distributions for five mice, each assayed on a different day after 21.25 Gy, from day 14 (labelled 1) to day 18 (labelled 5). The skin reaction at the time of assay was erythema for all five mice.

TABLE I

Percentage of mice assayed for microcolonies, and colony size

	Time after irradiation (days)											
	10	11	12	13	14	15	16	17	18	19	20	21
% of mice assayed	1	2	4.5	16.5	19	24.5	12	10	3.5	3.5	1.5	2
Colony No. – mean from all assay times	—	—	—	0.96 ±0.06	0.56 ±0.11	1.09 ±0.1	0.83 ±0.08	1.05 ±0.16	1.15 ±0.13	—	0.88 ±0.05	—
Mean No. of cells per colony	—	—	—	—	87±3.3	78±2.5	91±2.6	84±3.9	89±3.9	—	—	—

±1 Standard error

To demonstrate the validity of using a specified skin reaction level as the criterion for choosing the assay time for scoring colonies, rather than using a fixed time interval, the mice used over all the doses generating Fig. 5 were grouped according to the day they were assayed. At each time, the colony count for a particular mouse was divided by the mean count in the group of mice used at a given dose. The average values of these ratios at each day after all doses are given in Table I. The values do not increase significantly with the time of

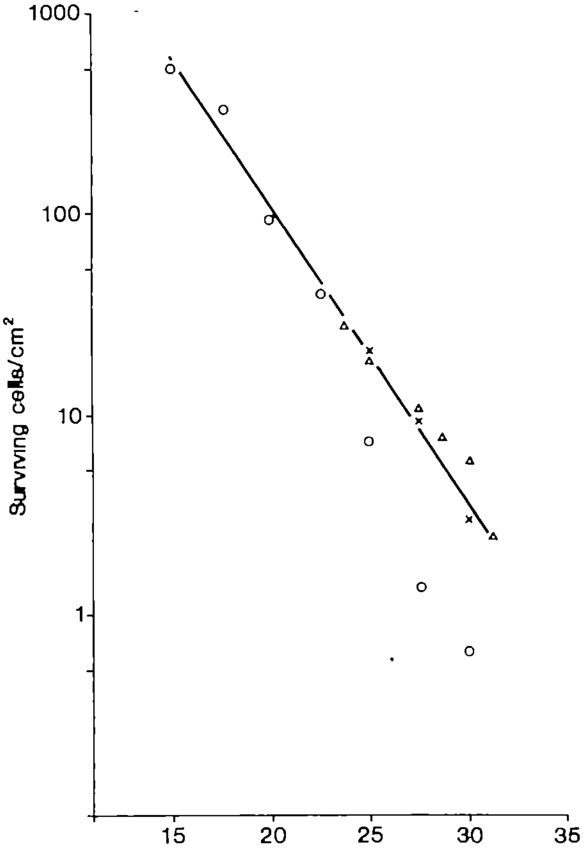

Fig. 3.

Surviving colony-forming cells per cm^2 versus radiation dose. Standard sampling errors are about 3% of the mean after the lower doses, increasing to about 30% after high doses. Tail skin assayed when showing erythema (○), with severe erythema (×) and with slight desquamation (△). Line fitted by eye through the circles up to 22.5 Gy, together with the crosses

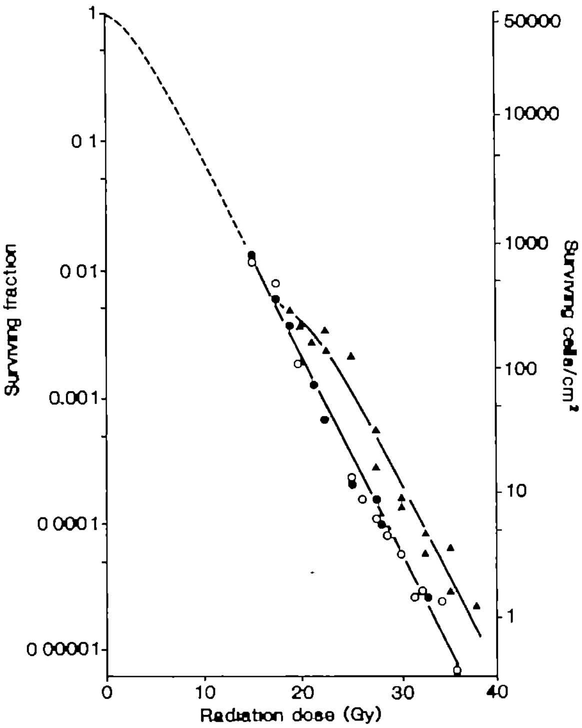

Fig 4

Survival after single doses (○, ●), and to a range of second doses given 24 h after a first dose of 17.5 Gy (△, ▲). The origin of the latter curve is the value of survival at 17.5 Gy on the curve fitted to the single-dose data. Open and closed symbols represent two separate experiments Sampling errors (not shown), as stated for Fig 3 The dashed curve represents the initial part of the single-dose curve, assuming it has the same shape as the initial part of the second-dose curve For survival parameters see text.

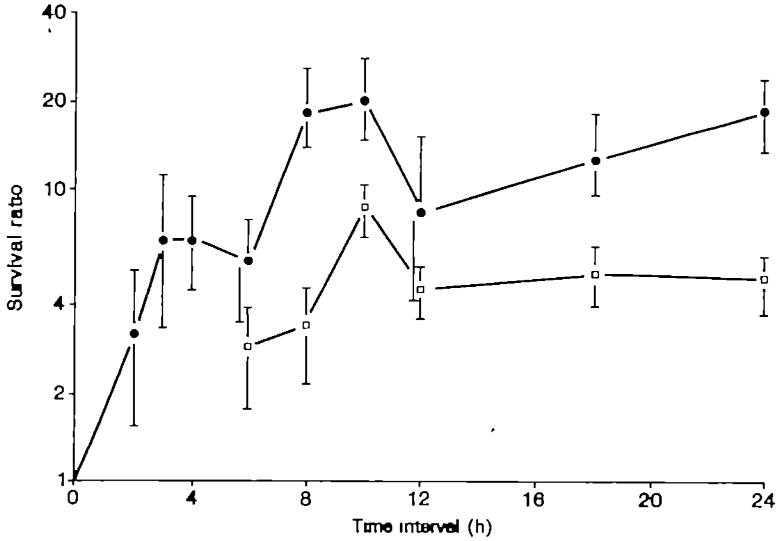

FIG 5.

Survival ratio versus the time interval, using two equal doses of 17.5 Gy. Present data (□); data taken from Withers (1967a) (●). Error bars are 95% confidence limits

assay. Also, in these same groups, the mean number of cells per colony is similar between assay times of 14 and 18 days (Table I). The frequency distribution of colony sizes is shown for five samples in Fig. 2, where a sample was assayed on each day from day 14 to day 18 after 21.25 Gy.

The single-dose survival curve measured in one experiment is shown in Fig. 3. When the criterion was erythema, there was a curvature in the survival data plotted on a log/linear graph (open circles). However, it was noticed that the colonies were generally smaller after high doses than after low doses. When the degree of skin reaction used as the criterion was increased to severe erythema, survival after high doses increased by a factor of about 5 (crosses). No further increase in survival occurred when a criterion of slight desquamation was used (open triangles). Also, at 23.5 Gy the level of survival using a criterion of slight desquamation followed the curve generated using erythema as the criterion, and hence this dependence of survival on the criterion used to determine the assay time was a feature only of the higher range of doses. After the lower range of doses, virtually all the colonies consisted of more than 32 cells when erythema had appeared. In subsequent experiments it was decided to use erythema as the assay criterion for doses up to 22.5 Gy, and severe erythema for higher doses. A criterion of severe erythema could not easily be used after both ranges of dose, because for doses less than 22.5 Gy there was some confluence of adjacent large colonies

The survival curve measured in two subsequent experiments is shown in Fig. 4 (left curve), using the above criterion. For the pooled single-dose data, $D_0 = 2.70 \pm 0.12$ Gy and n (right ordinate) $= 2.2 \times 10^5$ per cm^2. In order to produce a complete survival curve for these colony-forming cells, a split-dose experiment was performed where it was assumed that the response to a series of second doses, after a primary dose, reflected the response to solely the second doses (Hendry, 1979). First, two doses of 17.5 Gy were used, separated by intervals of time from 0 to 24 h (Fig. 5). On the basis of these results, it was decided to obtain a survival curve at 24 h after 17.5 Gy, which is shown in Fig. 4 (right curve) using data pooled from two experiments. The origin of the second-dose curve is the survival level at 17.5 Gy on the fitted curve for single doses ($D_0 = 3.13 \pm 0.29$ Gy; $n = 2.1 \pm 0.4$). The data are expressed as surviving colony-forming cells per cm^2 on the right ordinate, and as surviving fraction on the left ordinate. The latter procedure was accomplished by assuming that the second-dose curve reflected the initial shape of the single-dose curve (Hendry, 1979), shown as a dashed curve joining the single-dose curve to the origin in Fig 4. In this case the surviving fraction after a first dose of 17.5 Gy was assumed to be the same as that measured from 17 5 Gy given as a second dose (right curve, Fig. 4). Hence the total surviving fraction after both first and second doses could be calculated, and these are shown on the left ordinate in Fig. 4. The origin corresponded to 59 000 cells per cm^2 (right ordinate). The "complete' single-dose curve was characterised by $D_0 = 2.71 \pm 0.16$ Gy, a ratio of initial to final slopes of 0.35 ± 0.10, and $n = 3\ 8 \pm 1.4$ (left ordinate) or 2.2×10^5 cells per cm^2 (right ordinate).

The macrocolony data are shown in Fig. 6 (open circles) ($D_0 = 4.1 \pm 0.6$ Gy, and $n = 6.57 \times 10^3$ cells per cm^2). A discrepancy between the microcolony and macrocolony survival curves may be expected if there is coalescence of several microcolonies to form a macrocolony after the lower doses. This possibility was tested at several dose levels by counting the number of pairs (or groups) of microcolonies in a total of between 80 and 20 microcolonies (depending on the dose), where the distance between microcolonies was less than 3.05 mm (the average diameter of a macrocolony). When each pair was counted as one colony, predicted

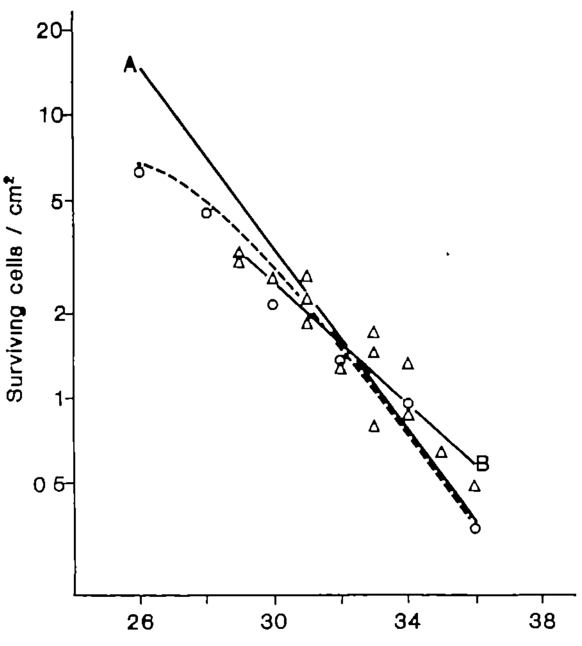

FIG 6

Macrocolony and microcolony survival data. (△) and line B, macrocolonies. Dashed curve, macrocolony survival predicted mathematically from the microcolony curve (see text). (○), macrocolony survival predicted from measurements of the distances between microcolonies (see text). Line A, taken from Fig 4.

values of macrocolony survival could be calculated, and these are shown as open circles in Fig. 6. A mathematical way to demonstrate this is to assume a Poisson distribution of surviving cells. If there are m microcolonies per cm^2 at a given dose, and the average area of a macrocolony is A, there are mA microcolonies in the average area of a macrocolony. The probability of there being only one microcolony in this area is $mA.\exp(-mA)$, and the probability of there being one or more than one microcolony is $[1-\exp(-mA)]$. Hence the number of macrocolonies will be less than the number of microcolonies by a factor:

$$\left[\frac{1-\exp(-mA)}{mA.\exp(-mA)}\right]$$

The factor tends to unity for low values of m. The expected number of macrocolonies at each dose (dashed curve in Fig. 6) was very similar to the number calculated using the measured distribution of the microcolonies described above. The survival curve for macrocolonies (curve B, Fig. 6) was above the curve for microcolonies after high doses. This was due to the greater weighting of the low-dose points because of the greater number of colonies scored. A similar exercise, calculating the (Poisson) probability of microcolonies arising from more than one microcolony, showed only a 6% underestimate of colony numbers at 15 Gy, decreasing to 1% at 20 Gy. This was due to the much smaller size of microcolonies compared with macrocolonies.

DISCUSSION

In the present technique, samples are taken for scoring microcolonies when the skin reaction has reached a specified level. This procedure was shown to give similar colony-size distributions among different samples assayed at various times after a given dose. This indicates that there is a direct relationship between the development of gross skin reactions and the growth of microcolonies.

TABLE II

SURVIVAL PARAMETERS OF EPIDERMAL COLONY-FORMING UNITS TO SINGLE DOSES

Site	Dose to give one colony/cm^2 (Gy)	Maximum test area (cm^2)	D_0 (Gy)	n/cm^2	CFU/cm^2	Reference
Macrocolonies						
Dorsum (plucked 1–12 h before irradiation)	20	1 13	1.37 (1.26–1.50)*	1.39×10^6	$\simeq 9 \times 10^4$	Withers, 1967 a, b
Dorsum (plucked 20–24 h before irradiation)	22	2.85	1 35 (1.20 – 1.55)*	1.35×10^7	$\simeq 2 \times 10^5$	Emery et al, 1970
Tail (unplucked)	34	1.7	4.10 ± 0.58†	6.57×10^3	—	Present data
Tail (unplucked)	34	1.4	3 45 ± 0.36†	$2\ 03 \times 10^4$	$\simeq$ 3 030	Hendry, 1984
Microcolonies						
Dorsum (plucked)	22	Whole body	2.33 ± 0.11†	1.23×10^4	—	Al-Barwari & Potten, 1976
Dorsum (unplucked)	—	—	4 4	4.6×10^3	—	Keech, 1982
Tail (unplucked)	33	1.7	2.70 ± 0.12†	2.24×10^5	$\sim 6 \times 10^4$	Present data

* 95% confidence limits.

† Standard error.

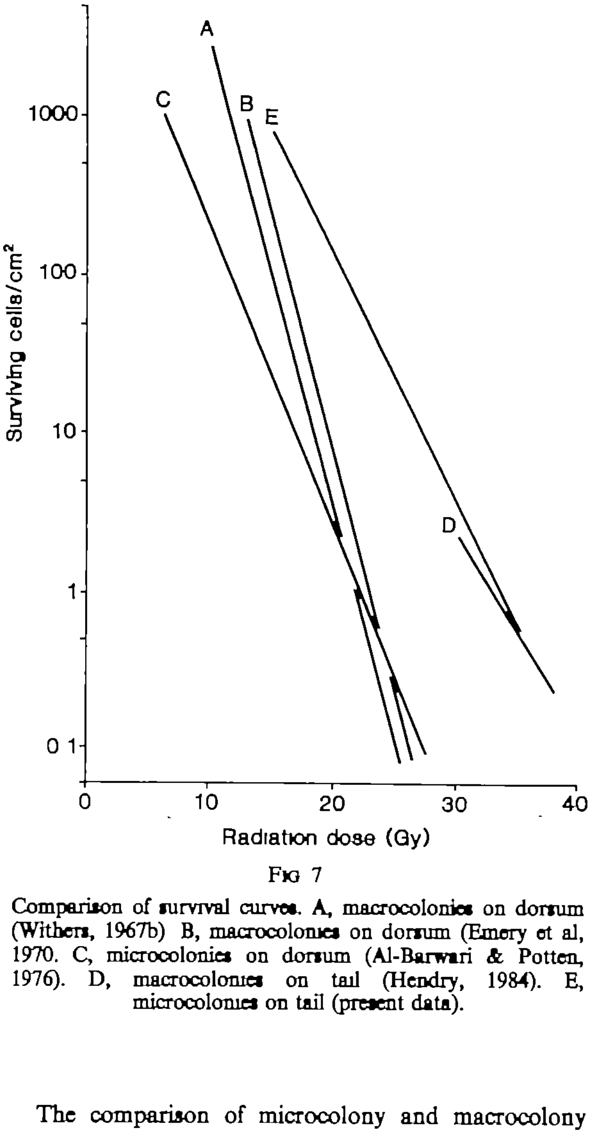

FIG 7

Comparison of survival curves. A, macrocolonies on dorsum (Withers, 1967b) B, macrocolonies on dorsum (Emery et al, 1970. C, microcolonies on dorsum (Al-Barwari & Potten, 1976). D, macrocolonies on tail (Hendry, 1984). E, microcolonies on tail (present data).

The comparison of microcolony and macrocolony survival curves demonstrates for the first time with epidermis that microcolonies containing more than 32 cells, *i.e.* where surviving colony-forming cells completed five divisions after irradiation, all develop into macrocolonies. Also, that in the low-dose range the macrocolony count is lower than expected because of the greater probability of several microcolonies surviving in the area covered by a single macrocolony. This accounts for the difference between the apparent sensitivity of macrocolony-forming cells, and the sensitivity of microcolony-forming cells, by a factor of 4 1/2.7 = 1.5 (Table II)

A comparison of survival curves for colony-forming cells reported in the literature is shown in Fig. 7. Curves A, B and D refer to macrocolonies, and C and E to microcolonies. Also, curves A, B and C pertain to dorsal epidermis, and D and E to tail epidermis. The curves for tail epidermis are displaced to higher doses compared to dorsum by about 10 Gy in the high-dose range. At lower doses the curve for tail converges towards the macrocolony curves for dorsum, but not towards the microcolony curve. It should be noted that the macrocolony technique for dorsum does not involve a correction for colony coalescence as is required with the present technique, and hence the comparison of these curves remains valid. Also, very few colonies were associated with hair follicle openings in the present work, in contrast to microcolonies in dorsum (Al-Barwari & Potten, 1976) and possibly also with macrocolonies in dorsum (discussed by Potten, 1985).

Reported survival parameters for epidermal colony-forming units are shown in Table II. The reason for the higher D_0 value for colony-forming cells in tail epidermis (D_0 approx. 2 7 Gy) or microcolonies in dorsal epidermis (2.3–4.4 Gy) compared with macrocolony-forming cells in dorsal epidermis (D_0 approx. 1.35 Gy) remains unknown. The number of CFU per cm^2 is calculated by reducing the extrapolation number by the recovery factor measured in split-dose experiments (*e.g.* Potten & Hendry, 1973). This factor was 3.8 at 24 h in the present studies, being the extrapolation number on the second-dose survival curve (Fig. 4). (A factor of 4.8 was measured in Fig. 5, and if 6 h or 10 h had been chosen instead, the factor might have been respectively lower or higher by at most a factor of 2.) The factor of 3.8 is lower than the factors of 15 to 18 (Withers, 1967a) and about 70 (Emery et al, 1970) calculated using dorsum. However, because of the lesser sensitivity of tail epidermal CFU, the corresponding values of (D_2-D_1) are more similar, namely 3.6 Gy (present data), 3.75 Gy (Withers, 1967a) and 5.7 Gy (Emery et al, 1970). The present data provide a value of 6×10^4 CFU per cm^2, which is slightly lower than, but of the same order as, the values reported by Withers (1967b) and Emery et al (1970). Using a value of about 2×10^6 basal cells per cm^2 of tail epidermis (Potten et al, 1982), a fraction of about 0.03 would be clonogenic, *i e.* CFU. This would represent a lower limit to the fraction if a radioresistant proportion of cells is being assayed. Also, a fraction of 0.03 would correspond to about five divisions of transit cells (*i.e.* $1/2^5 \sim 0.03$) in the basal layer (Potten, 1981), which would be an *upper* limit to the number of transit cell divisions if the proportion of CFU in the basal layer is truly higher.

Dose–response curves for macrocolonies are correlated with gross skin reactions (Hendry, 1984). The deduced sensitivity of target cells for epidermal healing was 2.8 ± 0.5 Gy, and this is now closer to the measured D_0 for colony-forming cells (2.7 ± 0.2 Gy) than the D_0 of 3.5 ± 0.4 Gy reported previously for macrocolony-forming units (Hendry, 1984). The close relationship described here between macrocolonies and microcolonies indicates that this microcolony technique can be used to study the cellular basis of epidermal responses in the tail in an accurate, quantitative way.

The technique is now being used with epidermis in other sites.

Acknowledgments

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Book reviews

The Ionising Radiations Regulations 1985 The Protection of Persons Against Ionising Radiation Arising from Any Work Activity. Health and Safety Commission, UK. pp. xii+40, 1985 (HMSO, London), £5 65
ISBN 0-11-883838-5

This EEC-stimulated document brings into operation a new regulatory system of protection in the UK, replacing the rather informal arrangements that have hitherto governed radiological safety. It considers the 35 Ionising Radiations Regulations (1985) and indicates how compliance is to be achieved by physical, engineering, procedural, administrative and educational means. Although the Code is not mandatory, failure to comply may be used as evidence in criminal proceedings.

A commendable feature is that the fundamental safety standards laid down by ICRP remain inviolate. The concept of "permissible" dose is now rightly superseded by that of dose limit, combined with a policy of keeping doses as low as reasonably achievable, or practicable. Readers should note that the Code explicitly defines those methods that should be considered "reasonably practicable". Their professional knowledge, skill and concern will, in future, need to be supplemented—not, one hopes, replaced—by the ability to digest complex technico-legal phraseology! The RPA will usually help as interpreter: the wise radiodiagnostician or radiotherapist will ensure that he is fully involved not just with safety but with the achievement of clinical goals.

Radiology is the largest man-made contributor to the collective radiation detriment—and probably to the collective benefit also. However, medicine is uniquely unamenable to control by regulation since it involves a subtle balancing of risks to the individual. The HSC acknowledges that special considerations apply to medical exposures and has made several welcome amendments following consultation Some specific difficulties remain, for example, dose-rate is sometimes elevated to a status unjustified by radiobiological evidence It is to be hoped that the HSC will encourage review of such problem areas.

This is an important document, which must be readily available to everyone in the UK with responsibility for the safe and beneficial use of radiation in medicine, industry, scientific research and education.

M. J. Day

Assessment of Radioactive Contamination in Man 1984. International Atomic Energy Agency, pp. 565+index, 1985 (IAEA, Vienna), 1140 Austrian Schillings.
ISBN 92-0-020085-0

This book contains the full texts of papers presented at an international symposium held in Paris in November 1984. The International Atomic Energy Agency is to be congratulated on the speed with which these proceedings have been published but the short time-scale has two consequences: the papers are published in the original language, only the abstracts of foreign-language papers being translated into English, and there is no record of the discussions that followed each paper.

This was the first symposium devoted to the assessment of radioactive contamination in man since one held in Stockholm as long ago as 1971 The meeting and the proceedings have, therefore, been eagerly awaited by those who are interested in new developments in techniques and in recent operational experience. They will find many papers of considerable interest The major areas of progress are: the increasing use of high-resolution, solid-state detectors in preference to low-cost, but poor-resolution, scintillators; methods of calibration for low-energy photons in the body, including phantoms, *in-vivo* procedures and the use of cadavers; improved methods both of detecting plutonium isotopes in urine and of interpreting the results; and the impact of the recommendations of the International Commission on Radiological Protection concerning limits on intake of radionuclides on the design of monitoring programmes and the interpretation of results.

The major area of difficulty remains the evaluation of exposure to uranium and transuranic radionuclides at levels less than the accepted limits. Adequate surveillance of worker exposure can only be achieved by complementary techniques of assessing airborne levels, monitoring excreta and direct measurements of radionuclides in the body. Although many papers were addressed to these techniques in isolation (possibly because of editorial limits on length), an impressive collection of papers on the uranium industry illustrates the success that can be achieved by comprehensive investigations.

In summary, all those concerned with monitoring and assessment of internal radiation exposure will find papers of interest in this volume.

F. A. Fry

1986, *The British Journal of Radiology*, 59, 397–398 APRIL 1986

Technical note

A modified Selectron vaginal applicator

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A standard treatment for corpus carcinoma in Glasgow is total hysterectomy combined with post-operative radiotherapy. Depending on the surgical findings, early cases (defined as Stage I), with fairly well differentiated tumours, penetrating less than one-third of the way through the myometrium, have been treated with a vaginal applicator loaded with three 10 mg Ra equivalent sources 6 weeks after surgery. All other stages, except IVB, were treated with 4 MV X rays to a "pelvic brick" followed by intracavitary treatment using a vaginal applicator loaded with three sources of 25 mg, 10 mg and 10 mg Ra equivalent respectively.

Initially, the brachytherapy sources were Ra "E" tubes supplied by the Radiochemical Centre, Amersham. In the early 1970s these were replaced by ^{137}Cs "G" tubes from the same supplier. The applicators, 62.5 mm long, were made from rubber tubing 21 mm in diameter. In 1980 a Selectron (Nucletron Trading, Leersum, The Netherlands) afterloading treatment unit was installed. At that time only one type of vaginal applicator was available from Nucletron. This consists of a series of perspex bobbins, available in different diameters, mounted on a straight metal tube. A perineal bar holds the bobbins in position and is tied to a waist bandage, to retain the complete applicator in the treatment position (Fig. 1). This vaginal applicator is modelled on the modified Fletcher–Suit applicator (Delclos et al, 1980).

In Glasgow, Selectron treatments were designed to replicate existing practice in all but dose-rate. Part of the standard technique was to introduce a layer of gauze packing posteriorly to reduce the dose to the recto-vaginal septum, which meant that the Selectron vaginal applicators still had to be introduced under a general anaesthetic in theatre. In addition, the Selectron applicator proved more difficult to pack, although at least the radiotherapist did not now receive any radiation exposure during the procedure.

THE MODIFIED APPLICATOR

In order to reproduce the previous treatment geometry and simplify the insertion technique, the Selectron vaginal applicator was modified. Nylon bobbins, 25 mm in diameter, were manufactured with holes drilled eccentrically 10 mm from the anterior surface; larger bobbins are available 30 mm in diameter, with the hole 12.5 mm from the anterior surface. The bobbins interlock with one another and the perineal bar, ensuring that the correct orientation of the applicator is maintained throughout treatment (Fig. 2).

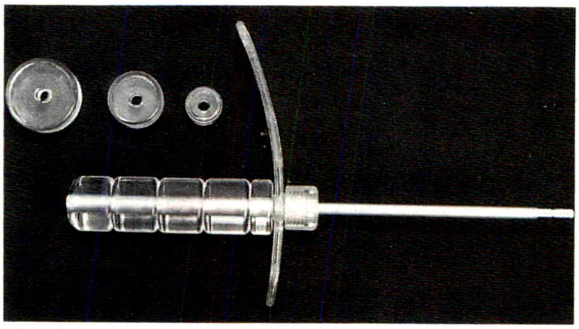


FIG. 1.

Selectron vaginal applicator.

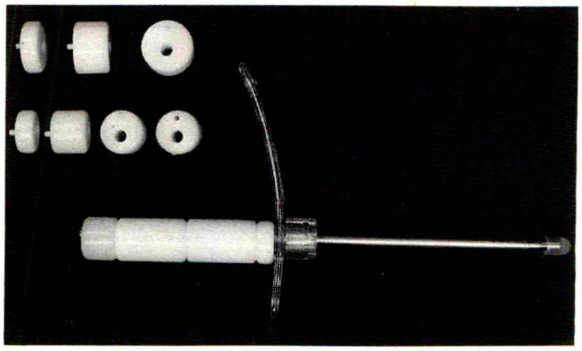
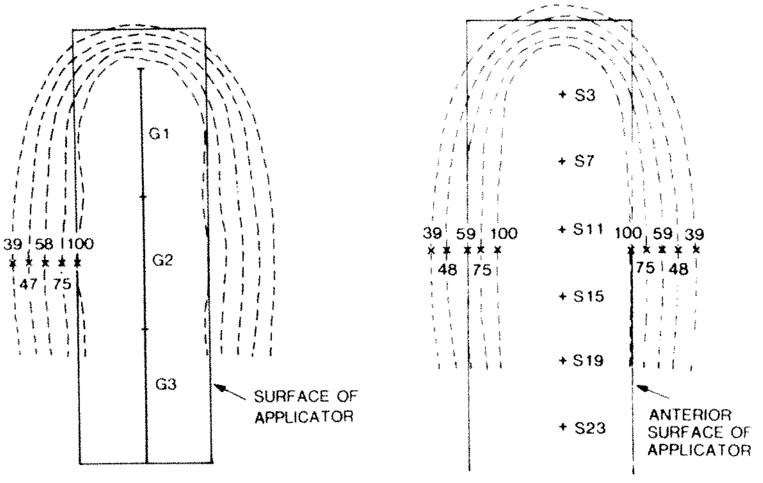


FIG. 2.

Modified Selectron vaginal applicators with 25 mm and 30 mm bobbins.



G1, G2, G3 - 10mg Ra equivalent Caesium G tubes

A

S3,S7, . . .S23 -active Selectron pellets

B

FIG. 3.

Comparison of dose distributions around vaginal applicators, doses are normalised to 100% on the anterior surfaces. (A) 10 mg Ra equivalent Cs "G" tubes loaded coaxially in a 21 mm diameter rubber applicator giving radially symmetric dose distribution. (B) Equivalent Selectron applicator with source train positioned eccentrically, 10 mm from the anterior surface of a 25 mm diameter bobbin. The eccentricity reduces the posterior surface dose to 59% of the anterior surface dose.

The gauze packing is thus replaced by 5 mm of nylon and the dose to the surface of the recto-vaginal septum is accurately predetermined.

In Fig. 3 the computed dose distribution around a modified Selectron vaginal applicator is compared with that from an applicator constructed using "G" tubes. The distributions are identical except near the tip of the applicators, where uncertainties in oblique filtration effects limit the accuracy of the treatment planning program. The dose-rate at 5 mm deep in tissue on the mid-point of the anterior surface varies with the size of the bobbin and the length of vaginal vault treated. Typically the dose at 5 mm depth posteriorly is 66% of that delivered at 5 mm depth anteriorly.

Use of this applicator offers the following advantages.

(a) The insertion of the applicator can be carried out in the Selectron treatment room. No theatre work is required and the associated high costs are saved.
(b) The patient is spared a general anaesthetic and treated at the convenience of the radiotherapist.
(c) The technique allows this relatively high-capital-cost unit to be better utilised, treating suitable vaginal cases between theatre sessions which can be reserved for the more difficult gynaecological insertions.

In a few patients, damage occurred at the lower end of the vagina and in these cases this was attributable to the lowest source being positioned too far down the source train. The comparatively high sensitivity of the tissues in the region of the introitus must be borne in mind, and the following precautions will reduce the likelihood of damage to this region. The lowest source is placed not less than 15 mm from the external urethral orifice. Waist bandages are firmly tied to the perineal bar to keep the applicator in the treatment position. The applicator position is checked regularly by the nursing staff during treatment to detect slippage. One of the major benefits of using the Selectron unit is that this can be done with no radiation exposure to staff.

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Case reports

Synovial chondromatosis of the hip joint presenting as a pathological fracture

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We describe an unusual case of synovial chondromatosis of the hip joint presenting as a pathological fracture, secondary to pressure erosion of the femoral neck, by the diseased synovium.

Synovial chondromatosis is an uncommon condition characterised by cartilaginous metaplasia of the synovial membrane. The cartilaginous bodies so formed may remain attached to the synovium or sequestrate into the joint cavity to form loose bodies (McIvor and King, 1962).

The usual methods of presentation are pain, crepitus, joint swelling, locking, or as a mass lesion (Jeffreys, 1967; Milgram 1977).

The diagnosis is usually confirmed on a radiograph, and therefore it is important to recognise the condition as early as possible, so that complications are avoided.

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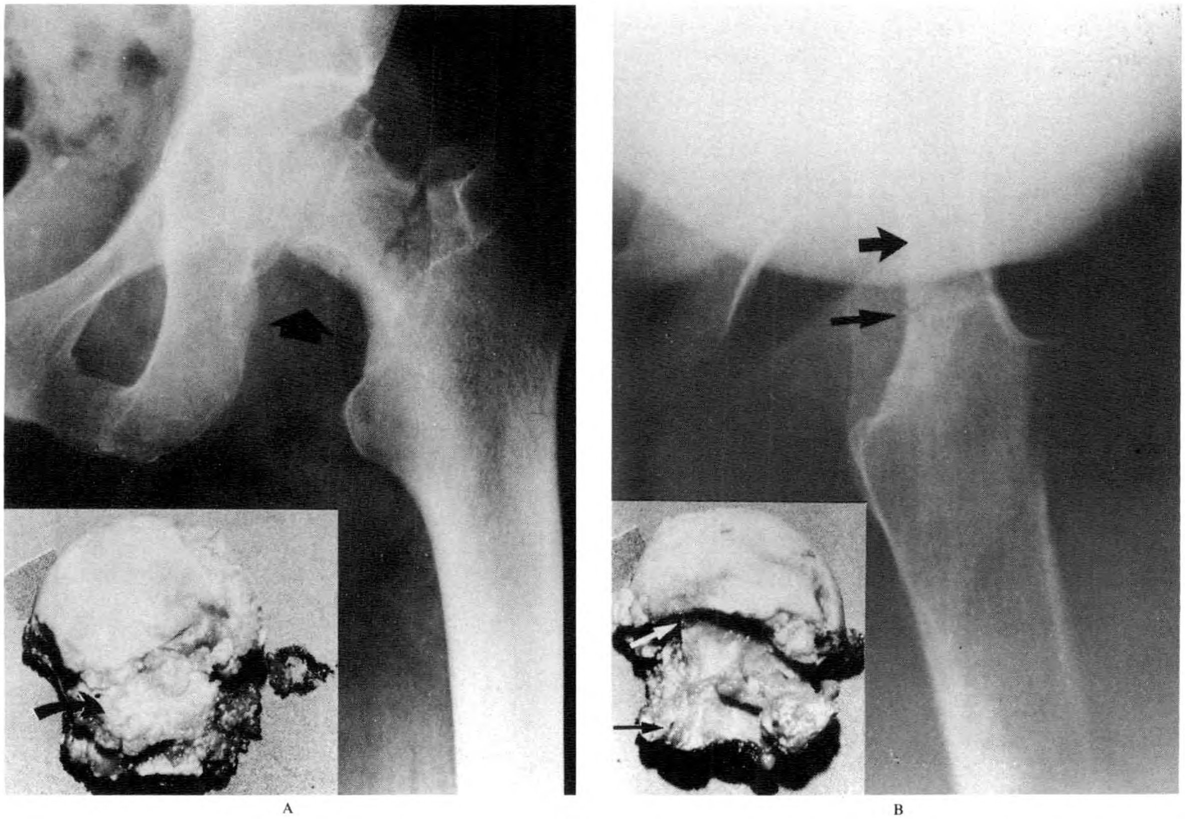

FIG. 1.

(A) Antero-posterior view of the left hip on presentation. The arrow indicates specks of calcification corresponding to the area arrowed in the pathological specimen (inset). (B) Lateral view of the left hip showing thinning of the femoral neck. The arrows correspond to those seen in the pathological specimen (inset).

CASE REPORT

A 55-year-old, white female presented with sudden onset of severe disabling pain in the left hip after bending down to lift a suitcase.

She gave a 5-year history of milder pain in the same hip and a previous radiograph of the hip taken nearly 3 years earlier had been interpreted as showing changes of osteoarthritis.

On examination, there was a full range of movement of her right hip whereas on the left hip, flexion was limited to 70 degrees, and, because of pain, internal and external rotation were not possible. The remainder of the clinical examination was normal.

Radiographic examination (Fig. 1A) revealed an undisplaced transcervical fracture, with marked cortical scalloping superiorly and inferiorly at the cervico-capital junction. Thinning of the femoral neck was seen most dramatically in the lateral radiograph (Fig. 1B). In addition, small specks of calcification were noted inferior to the femoral neck and radiolucent areas could be seen in both the acetabulum and the femoral head, together with a moderate degree of protrusio acetabuli.

In retrospect, scalloping of the femoral neck, radiolucencies in the acetabulum and femoral head and protrusio acetabuli, together with flecks of calcification inferior to the joint, were all present on the original radiograph (Fig. 2).

At operation, gross synovial chondromatosis was found, filling the capsule and causing obvious pressure erosion of the femoral neck, which was only half its expected diameter (Fig. 1B). The medial wall of the acetabulum was also eroded by cartilaginous material but this had not penetrated into the pelvis. A fracture was confirmed in the mid-cervical region.

Extensive removal of the diseased tissue was performed and a Muller total hip replacement was inserted by the standard techniques, using polymethylmethacrylate cement. The post-operative course was satisfactory.

Pathological examination of the surgical specimen revealed firm, nodular cartilaginous tissue encasing the femoral neck (Fig. 1A) causing erosion and thinning of the bone (Fig. 1B), particularly at the junction of the head and neck. The histological features were typical of synovial chondromatosis.

DISCUSSION

Synovial chondromatosis may occur in any diarthrodial joint and is usually monarticular, affecting the knee more commonly than the hip (Bloom and Pattinson, 1951), occurring typically in men in the third or fourth decades of life; it is rare before puberty (Pelker et al, 1983).

The aetiology is unknown but it is accepted by Jaffe (1958), Jeffreys (1967) and many other authors that the condition represents a benign neoplasm. Although malignant change has been recorded, it is exceedingly rare (Mullins et al, 1965).

Milgram (1977) proposed that the disease represents a reactive process of the synovial membrane, which follows a temporal sequence characterised by recognised phases:

(1) active intrasynovial disease, with no loose bodies;
(2) transitional lesions with both active intrasynovial proliferation and free loose bodies; and
(3) multiple free osteochondral bodies with no intra-synovial disease.

In this respect it would seem to be a self-limiting intrasynovial process and, therefore, may not demand active treatment if joint function is not significantly disturbed.

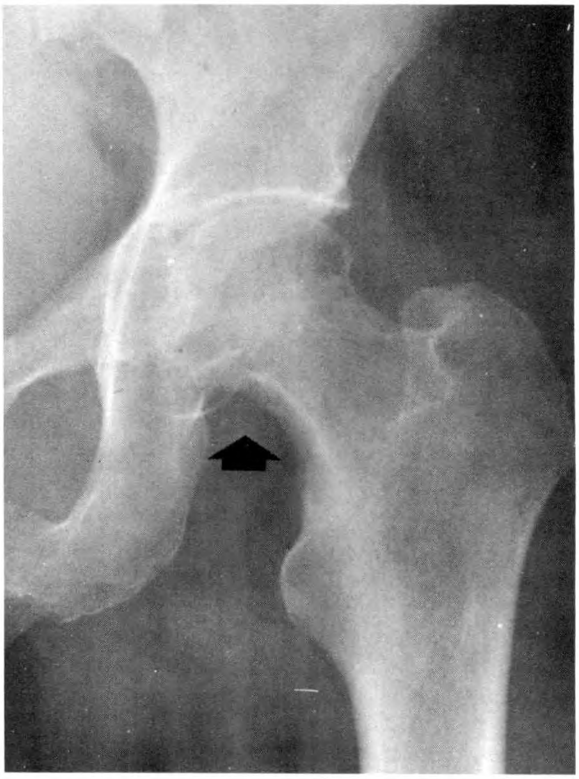

FIG. 2.

Antero-posterior view of the left hip 27 months earlier. The arrow indicates faint specks of calcification.

Our patient presented with a pathological fracture through the femoral neck, which had been extensively weakened by pressure erosion. This feature of the disease has been previously described, and noted to return to normal on removal of the diseased tissue (Bloom and Pattison, 1951).

If the disease had been recognised earlier, when the patient first presented, partial synovectomy and removal of the loose bodies (Jeffreys, 1967) may have avoided the more serious complication of femoral neck fracture which, to the authors' knowledge, has been described in only two previous cases of synovial chondromatosis (Norman and Steiner, 1984).

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Mycotic aneurysm of the renal artery: CT appearance

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Mycotic aneurysms of the renal artery are rare with the diagnosis usually made by angiography (Clark et al, 1972; Kaufman & White, 1978). Computed tomographic diagnosis of abdominal mycotic aneurysms has been discussed (Pripstein et al, 1979), but to date the CT appearance of a renal artery mycotic aneurysm has not been reported. Mycotic aneurysms are uncommon and difficult to differentiate on CT from an aortic dissection with involvement of the renal artery. However, renal artery mycotic aneurysms should be considered, given the appropriate clinical circumstances. We report a case of a pathologically proven main renal artery mycotic aneurysm.

CASE REPORT

A 66-year-old white man was admitted with right lower quadrant tenderness, fever, and leukocytosis. His urinalysis indicated three to five white blood cells per low power field and the rare occurrence of bacteria He had a longstanding history of chronic urinary tract infections secondary to benign prostatic hypertrophy, and the urinalysis findings were considered his baseline. Blood cultures were drawn on admission Because of increasing abdominal pain over the next 24 h, a laparotomy with appendicectomy was performed. At surgery the liver, gallbladder, duodenum, and spleen were normal. Microscopically the appendix showed no inflammation. The blood cultures at this point showed no growth.

In the post-operative period the patient developed bilateral flank pain, fever, and positive staphylococcal urine and blood cultures. The pre-operative blood cultures were subsequently staphylococcal positive An intravenous urogram showed normal function of the right kidney with non-visualisation of the left kidney An intravenous urogram performed 2 months previously was normal. Ultrasound revealed diffuse enlargement of the left kidney without calyceal dilatation A CT scan of the abdomen and pelvis showed a large irregular soft-tissue mass in the left retroperitoneum between the aorta and kidney. Following an intravenous bolus of contrast medium there was immediate enhancement of both an irregular central portion and a more eccentric region to the left. The left kidney did not function (Fig. 1). An angiogram indicated delayed flow to the left renal artery with the late appearance of an oval contrast collection diagnostic of an aneurysm (Fig. 2).

The patient was re-explored and a large contained rupture of a left main renal artery aneurysm was found. The abdominal aorta was not involved. Pathologically the left main renal artery was dilated and contained purulent material. There was an inflammatory infiltrate in the aneurysm wall. The perirenal area contained numerous small staphylococcal abscesses.

The patient did well after surgical removal of the kidney to include aortic patch graft placement. He eventually underwent a transurethral prostatectomy without complication.

DISCUSSION

The term "mycotic aneurysm" now includes any infectious process involving any or all layers of an arterial wall. The aneurysm may develop as a result of septic embolism, infection of an atheromatous plaque, or spread from a contiguous area of inflammation. The aorta is the most common site of involvement and bacterial endocarditis continues to be the primary predisposing factor, although such aneurysms may occasionally be seen after vascular surgery or trauma (Stengel & Wolferth, 1923; Kaufman & White, 1978; DuBrow & Patel, 1981).

Mycotic aneurysms of the renal artery are rarely reported in the literature, although they have been

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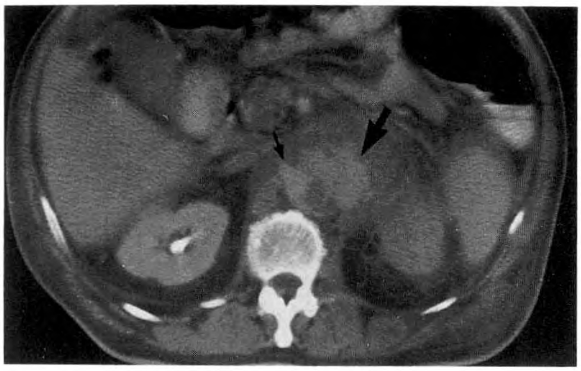

FIG. 1.
Computed tomographic scan through upper portion of kidneys after bolus injection of intravenous contrast medium. Soft-tissue mass medial to left kidney with central collection of contrast in aortic lumen (small arrow) and lateral collection in lumen of renal artery mycotic aneurysm (large arrow).

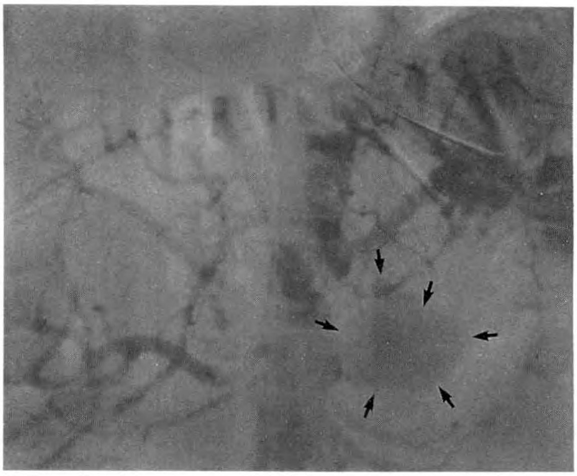

FIG. 2.
Subtraction film from an abdominal aortogram shows large oval contrast collection in lumen of dilated left renal artery mycotic aneurysm (arrows).

described in all age-groups (Clark et al, 1972, 1975; Kaufman & White, 1978). Of the 382 mycotic aneurysms that Stengel and Wolferth collected (1923), only five involved the renal artery or its branches. In separate case reports, Clark et al (1972, 1975) reported two intrarenal mycotic aneurysms with the associated angiographic findings, one of which was associated with staphylococcal septicaemia. The combined angiographic and excretory urographic findings in three pathologically unproven small intrarenal mycotic aneurysms have also been described (DuBrow & Patel, 1981).

Computed tomography has been of diagnostic use in mycotic aneurysms of the abdominal aorta (Pripstein et al, 1979), but to date the CT appearance of a pathologically proven renal mycotic aneurysm has not been reported. Despite claims that it is not possible to distinguish between mycotic, medial degenerative, or atherosclerotic disease of the renal artery (Haaga & Patel, 1983), an irregular mass with central enhancement near the renal pedicle and impaired renal function in a patient with septicaemia and bacteriuria should cause a renal mycotic aneurysm to be suspected. Accurate and early diagnosis is vital because of the high mortality associated with this disease (Kaufman & White, 1978).

Mycotic aneurysms are most often diagnosed by the angiographic finding of arterial dilatation with a history of bacterial endocarditis and associated visceral signs and symptoms. The renal artery mycotic aneurysm in this patient probably developed from the nearby perirenal abscesses found at surgery. In a patient with longstanding urinary tract infections it is not difficult to postulate that pyelonephritis developed with secondary perirenal abscesses and infection of the contiguous main renal artery. In this patient the aneurysm was probably present at the time of the initial laparotomy because of the positive pre-operative blood cultures and septic presentation. A contrast-enhanced CT scan of the abdomen prior to the initial surgery would have localised and identified the pathological process immediately. Angiography would have confirmed this and appropriate management would have been accomplished at the initial laparotomy.

Aneurysms of the renal artery are reported to cause referred pain to the anterior abdomen in a pattern similar to renal colic caused by ureteral stones or renal infection (Abeshouse, 1951). It is hard to explain why this man had referred pain on the contralateral side unless a superimposed pyelonephritis on that side was the cause of the right lower quadrant pain. Mycotic aneurysms of any artery can have perplexing clinical presentations (Cliff et al, 1970; Kaufman & White, 1978), and this case may add to the list of unusual clinical presentations for this entity.

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Diagnosis of spontaneous aorto-caval fistula by computed tomography

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Spontaneous aorto-caval fistulae are an uncommon complication of abdominal aortic aneurysms. The diagnosis may not be apparent at the initial clinical examination, as the fistulae have variable clinical features. Arteriography has been used to establish this diagnosis (Dardik et al, 1976; Fyfe et al, 1978; Gregson et al, 1983). We report a case in which the diagnosis was established by computed tomography (CT). This is believed to be the first report of this condition shown by CT.

CASE REPORT

A previously fit 67-year-old male presented with a 4-day history of chest pains, dyspnoea and dizziness. On examination he appeared unwell, with a blood pressure of 100/60 mmHg and a regular pulse rate of 100 per min. There was a large, pulsatile abdominal mass with a bruit over it. The peripheral pulses were normal and there was no ankle oedema; the feet, however, were cyanosed.

The presence of an abdominal aortic aneurysm was confirmed by ultrasound examination and, as this suggested that the aneurysm arose above the renal vessels, a pre-operative CT scan was performed. A rapid sequence scan was made during injection of a bolus of 100 ml of non-ionic contrast medium through an arm vein.

On CT the aneurysm measured 9.8 cm in maximum diameter (Fig. 1). The inferior vena cava was dilated, measuring 3.5 cm at the level of insertion of the hepatic veins. On the early scans there was significantly greater enhancement of the inferior vena cava (109 HU) in comparison with that of the aorta at the same level (86 HU) (Fig. 2). Because of the increased attenuation on the venous side after injection via the arm, a diagnosis of spontaneous aorto-caval fistula complicating the aortic aneurysm was made; there were also small bilateral pleural effusions, presumed to be due to high-output failure from the fistula.

At operation a fistula measuring 2 cm was found between the distal aorta and the inferior vena cava. This was closed and a dacron trouser graft inserted to treat the aneurysm. The patient made a rapid and uneventful recovery and was discharged 2 weeks after operation.

DISCUSSION

Aorto-caval fistulae may develop after aortic trauma such as lumbar disc surgery, penetrating stab wounds and gunshot wounds (De Bakey et al, 1958; Gregson et al, 1983). Less commonly they may occur spontaneously with rupture of an abdominal aortic aneurysm into the inferior vena cava. De Bakey et al (1958) reported a 0.9% incidence of associated fistulae in a series of 460 cases of aortic aneurysm treated

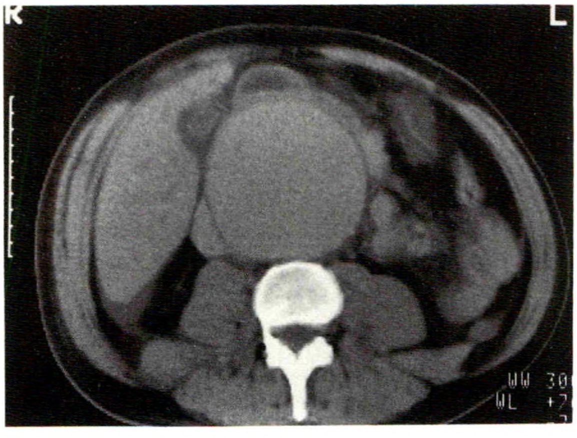

FIG. 1.

Transverse section at level of the third lumbar vertebra, showing huge aortic aneurysm of diameter 9.8 cm.

Author for reprints: Dr R. Clements.

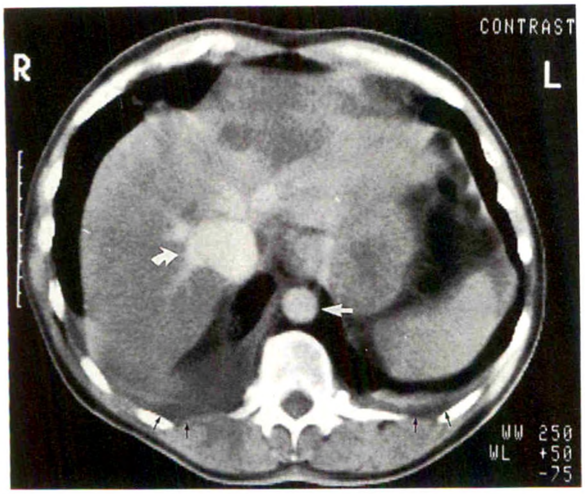

FIG. 2.

Denser contrast within the dilated inferior vena cava (curved arrow) than the aorta (straight white arrow). An incidental finding is a simple hepatic cyst. Small basal effusions (black arrows) are present, due to high output failure resulting from the fistula.

surgically. Lippey and de Burgh (1978) estimated that by 1978 there had been 98 documented cases in the literature.

Spontaneous aorto-caval fistula results in gross haemodynamic changes; a successful outcome is more likely if the diagnosis is established pre-operatively (Burke & Jamieson, 1983).

A variety of clinical features have been described in this condition. Cortis et al (1972) described a diagnostic triad of a pulsatile abdominal mass, severe low-back pain and a continuous abdominal bruit. This triad is seen in 50% to 90% of cases (Gregson et al, 1983; MacLellan & Roberts, 1983). Other features are those of a large arterio-venous fistula. The cardiac features of this may present as congestive cardiac failure, while the systemic venous effects may cause lower-limb cyanosis, haematuria, rectal bleeding or priapism (Burke & Jamieson, 1983).

Pre-operative arteriography has been shown to be of value by several authors (Dardik et al, 1976; Fyfe et al, 1978; Gregson et al, 1983). It confirms the clinical diagnosis and demonstrates the site of the fistula which, when spontaneous, is almost always between the distal end of the aneurysm and the lower inferior vena cava.

Computed tomography has been shown to be a useful technique in the pre-operative assessment of abdominal aortic aneurysm. This case demonstrates its use in establishing the diagnosis of aorto-caval fistula complicating an aneurysm. The aortic and vena caval dilatation is well demonstrated. On dynamic scanning the rapid flow of contrast medium from the arterial side into the dilated inferior vena cava is characteristic of a fistula. The precise site of the fistula was not, however, demonstrated.

Computed tomography is a much less invasive technique than arteriography and we feel that it should be the investigation of choice for confirming the presence of an aorto-caval fistula.

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Case reports

Calcified gastric cancer: report of a case and review of literature

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Calcification within gastric cancer is a rare occurrence and a limited number of cases have been reported in the English literature (Robertson & Osterhout, 1952; Batlan, 1954; Kendig et al, 1957; Matthews et al, 1958; Petersen, 1958; Butler, 1959; Khilnani, 1960; McGinnis, 1960; Gemell, 1964; Hermann & Rozin, 1964; Berezowski, 1965; Thomas & Rice, 1967; D'Altorio, 1973; Nishimura et al, 1984). Computed tomography (CT) findings have been described once (Nishimura, 1984). Histologically, all reported cases corresponded to a mucinous adenocarcinoma.

CASE REPORT

A 45-year-old woman was admitted with a history of epigastric pain, anorexia, nausea and vomiting. A plain abdominal radiograph revealed the presence, in the left upper quadrant of the abdomen, of numerous tiny punctate calcifications, roughly outlining the fundus and the body of the stomach (Fig. 1). A repeat abdominal radiograph, after a gas-releasing agent, showed the localisation of the calcific nodules within the gastric wall (Fig. 2).

A double-contrast barium examination of the upper gastrointestinal tract was performed and this demonstrated a large infiltrating lesion involving the fundus and proximal stomach, with tiny homogeneous calcifications distributed within the mass (Fig. 3).

An upper gastrointestinal endoscopic examination showed a normal oesophagus and a gastric lesion suspected of being malignant; biopsies disclosed a mucinous adenocarcinoma.

A CT study, performed for a pre-operative staging of the malignancy, confirmed the thickening of the gastric wall and the miliary calcifications within it (Fig. 4). There was no evidence of lymphadenopathy along the lesser curvature or of liver metastases, and the pancreas and peritoneum appeared free of neoplastic dissemination. At laparotomy, an infiltrating carcinoma involving the proximal half of the stomach was found. There was no intraperitoneal seeding or involvement of para-aortic lymph nodes. Total gastrectomy, splenectomy and oesophago-jejunostomy were performed. The patient made an uneventful recovery.

DISCUSSION

Calcification in gastric adenocarcinoma is infrequent. The first autopsy report of calcified gastric adenocarcinoma was by Fukuda in 1922. In the English literature, the earliest case of calcified mucus-secreting adenocarcinoma demonstrated radiologically was described by Weston in 1900. A peculiar aspect of the lesion is represented by its occurrence in the mid-1940s (D'Altorio, 1973). A review of the literature substantiated that the localisation at the fundus has been described by a few authors (Abel, 1939; Batlan,

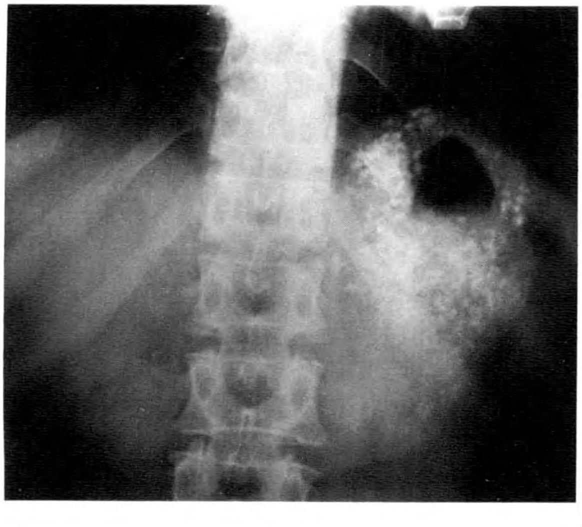

FIG. 1.

Plain abdominal radiograph showing punctate calcification overlying the region of the gastric fundus and body.

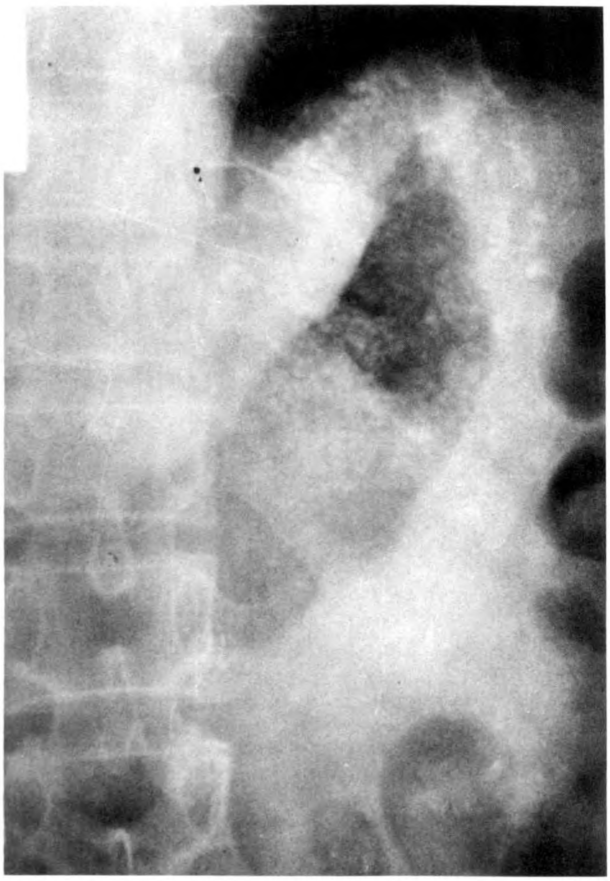

FIG. 2.

After administration of an effervescent agent, the distribution of the calcification appears to be in the gastric wall.

1954), while the distal stomach was more frequently affected in other reports (Imbert, 1931; Robertson & Osterhout, 1952; Kendig et al, 1957; Matthews et al, 1958; Butler, 1959; Gemell, 1964; Thomas & Rice, 1967; D'Altorio, 1973; Yasuma et al, 1973; Murayama et al, 1982). Each case described is a mucinous adenocarcinoma. The calcification is of a fine punctate or miliary nature, outlining the tumour mass.

The size of each area of calcification has been described usually as being 1–3 mm. A similar pattern of calcification has also been found in some cases of mucinous adenocarcinoma of the colon and of the ovary. Benign tumours of the stomach, such as leiomyomas and haemangiomas, may calcify, but in these cases, the areas of calcification are usually more dense and patchy (Garbarini, 1950; Leigh, 1950).

There are several theories as to the aetiology of the calcification. The most plausible one is that it is dystrophic calcification of ischaemic and necrotic areas owing to the relative alkalinity of the circulating extracellular fluid. The alkalinity is a consequence of diminished cellular respiration with reduced carbon dioxide production as a result of ischaemia. Prolonged vomiting could also raise the stomach pH (D'Altorio, 1973). Batlan (1954) also suggested that mucin, a glycoprotein, would act like cartilage in growing bone and, thus, have a greater tendency to calcify, by enhancing deposition of calcium.

Calcification in the left upper quadrant may be found: in the spleen secondary to old granulomatous disease; in the pancreas in chronic pancreatitis; in the left kidney in nephrocalcinosis and hypernephroma; in the adrenal gland in old tuberculosis and adrenal carcinoma; in lymph nodes; in blood vessels and in retroperitoneal sarcoma. Some cases of gastric leiomyoma and leiomyosarcoma also calcify. Gastric calcification has

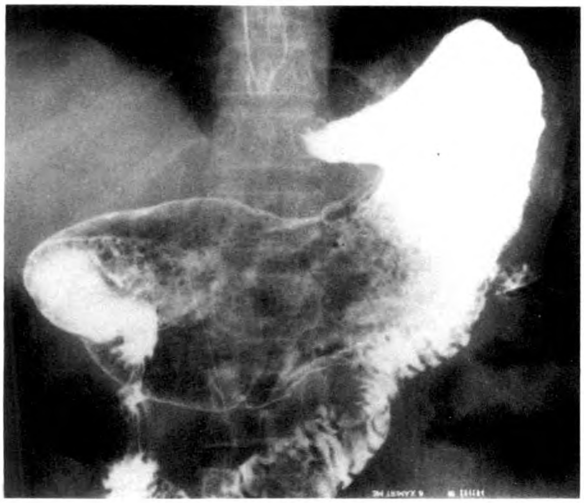

FIG. 3.

Double-contrast barium meal confirms the intramural distribution of the calcification at the fundus and proximal portion of the body of the stomach, with thickening of the gastric wall.

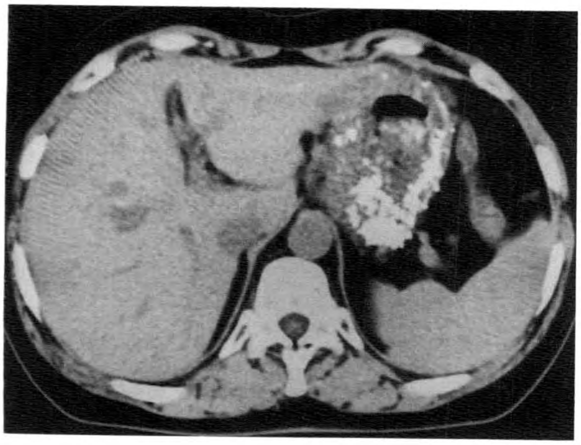

FIG. 4.

Unenhanced CT scan, without the use of an oral contrast agent, shows a thickened gastric wall with punctate calcification. No hepatic metastases seen.

also been described as part of the visceral calcification in renal osteodystrophy (Greenfield, 1980).

In the above case, the punctate calcification in the thickened wall of the stomach was sufficiently characteristic on the plain radiograph, especially after administration of the effervescent agent, to permit diagnosis with reasonable accuracy. The CT examination, apart from confirming the intramural distribution of the calcification, also excluded extragastric infiltration of the tumour and presence of lymph-node and hepatic metastases. The punctate calcification strongly suggested mucin-producing adenocarcinoma and was thereby differentiated from the circumscribed and patchy-type calcification found in leiomyomas and leiomyosarcomas.

It is not known why only a small percentage of gastric cancers calcify, but almost all of the calcium-producing gastric cancers, including the above case, were mucinous adenocarcinomas. The only other tumours of similar histology that occasionally calcify are the ovarian papillary mucoid and cystic mucoid adenocarcinomas, as well as mucin-producing colonic carcinomas.

ACKNOWLEDGMENTS

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Case reports

Computed tomographic and pathological findings in pulmonary alveolar microlithiasis

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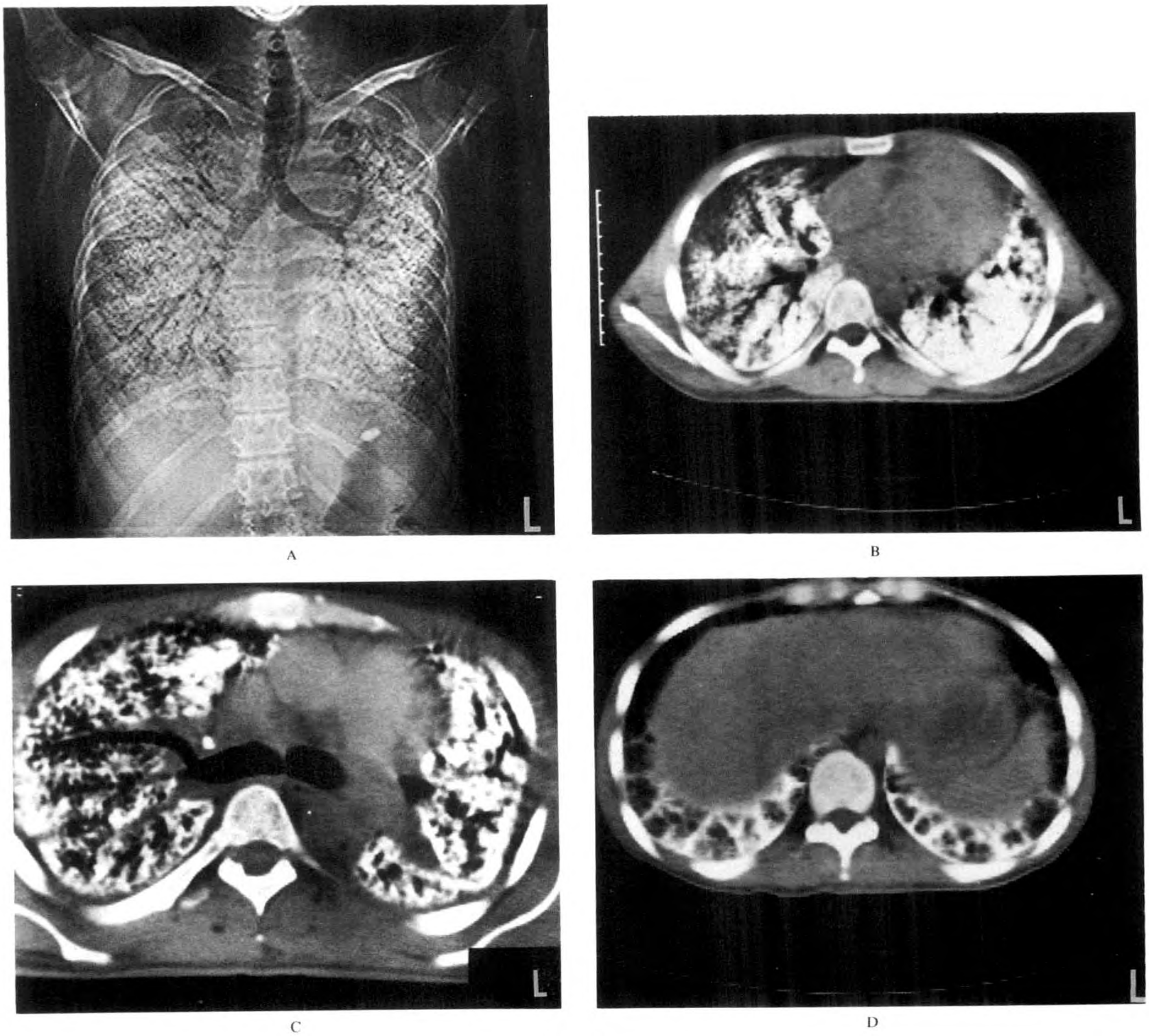


FIG. 1.

(A) Digital slit-beam radiograph ("Scanogram") of chest showing widespread dense calcification and apical pleural caps (L + 109, W 400). (B) Section 12 mm thick showing posterior distribution of calcification (L + 62, W 600). (C) Section 6 mm thick in mid-thorax showing pleural thickening along the chest wall, adjacent to the descending aorta, and into the oblique fissure on the left (L + 138, W 600). (D) Section 12 mm thick at lung base showing dense calcification along the line of the visceral pleura (L + 62, W 600).

Pulmonary alveolar microlithiasis is a rare condition characterised by widespread intra-alveolar calcification. Although the clinical and radiological features have been well described (Sosman et al, 1957), there are few reports of the computed tomographic appearances (Winzelberg et al, 1984). We report the CT and pathological findings in a patient with the typical plain-radiographic features of pulmonary alveolar microlithiasis.

CASE REPORT

A male Pakistani patient was first seen in 1962 at the Leeds Chest Clinic aged 13 years. Although he was asymptomatic, a chest radiograph showed the characteristic features of pulmonary alveolar microlithiasis. On presentation for a routine chest radiograph 16 years later he remained symptom-free. Over the next 5 years he developed progressive shortness of breath which became increasingly severe during the 2 months prior to admission. By then there was evidence of finger clubbing, weight loss and bilateral basal crepitations. His admission radiograph showed widespread, almost confluent, calcification with obliteration of the mediastinal contours. Following initial treatment of a chest infection and because of increasing respiratory embarrassment, a course of bronchial lavage was commenced. After the first lavage a CT scan was performed (Fig. 1).

Computed tomographic findings

The patient was examined in the supine position and 12 mm thick sections were obtained from T3 to T11. Calcification was most prominent at the bases, adjacent to the mediastinum and posteriorly. A bulla was present in the left upper lobe. A striking feature was the presence of soft tissue between the ribs and the calcified parenchyma. Similar masses of soft-tissue attenuation were noted adjacent to the cardiac borders, parallel to the major bronchial subdivisions and extending into the greater fissure on the left. These areas of soft-tissue attenuation were considered to represent pleural fibrosis or organised pleural fluid. On the lower sections, a thin line of calcific attenuation abutted the lung surface, suggesting calcification of the visceral pleura.

Three bronchial lavages were performed and on each occasion sand-like material containing hydroxyapatite was removed. A repeat CT scan showed no change in the overall appearances. For an objective assessment of any improvement following lavage, lung attenuation measurements were performed. By using a strain-gauge chest-wall monitor as described by Robinson and Jones (1982), attenuation measurements were obtained at the same degree of lung expansion and, as near as possible, to the same anatomical position on the two occasions. The results are given in Table I. The mean lung attenuation values were grossly elevated, being similar to those of vertebral trabecular bone.

TABLE I

MEAN LUNG ATTENUATION MEASUREMENTS (HU)*

	Examination 1		Examination 2	
	R lung	L lung	R lung	L lung
Upper	+92	+98	+96	+101
Middle	+90	+98	+97	+104
Lower	+89	+96	+93	+105
Mean of three sections	+90	+97	+95	+103

*Normal range (Chalmers et al, in preparation): -765 ± 29 (SD).

Bronchial lavage resulted in no clinical or radiological improvement in this patient. The subsequent clinical course was characterised by repeated and intractable pneumothoraces. Death occurred 6 months after presentation.

Pathological findings

At post-mortem examination the features of interest were restricted to the thoracic organs. The lungs, which did not collapse, showed patchy nodular thickening of the visceral pleura which extended into the interlobar fissures (Fig. 2). Subpleural emphysematous bullae up to 5 mm in diameter were apparent. The lungs had a combined weight of 3100 g (normal weight, 1200 g) and were uniformly "gritty" on sectioning. The cut surface had the texture of fine sandpaper and all segments appeared equally affected.

The heart (450 g) showed features of cor pulmonale with considerable right ventricular hypertrophy, the right ventricular wall measuring 8 mm (normal thickness < 4 mm). The

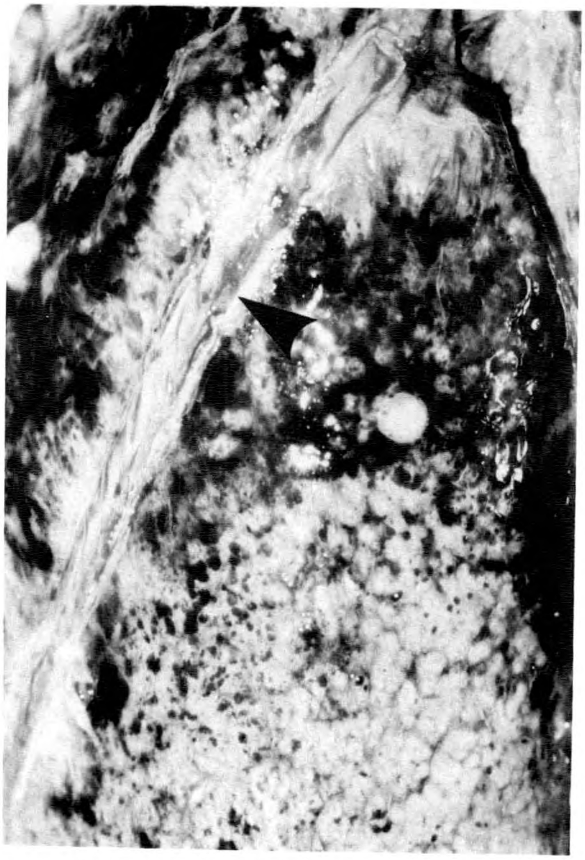
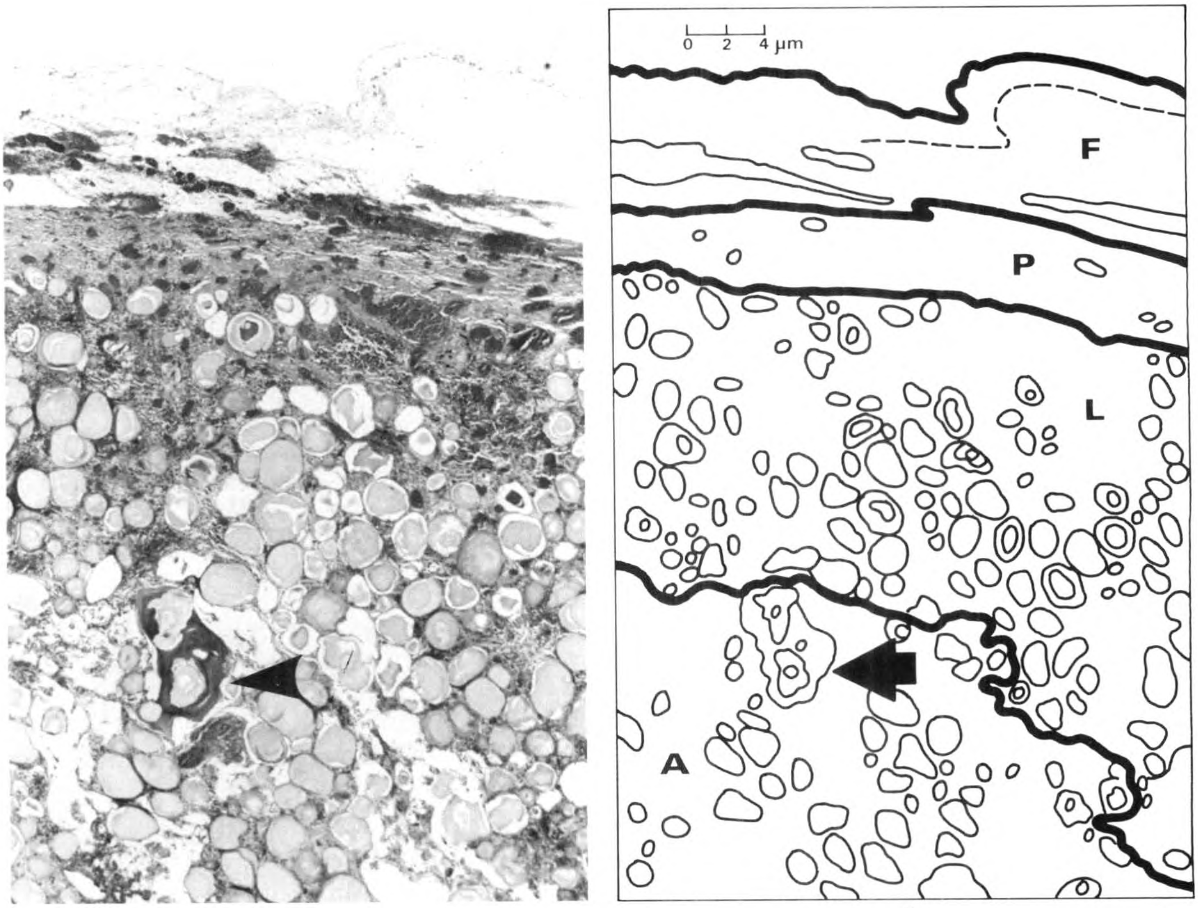


FIG. 2.

Macroscopic post-mortem appearance of the lateral aspect of the left lung. There is patchy nodular pleural thickening, which extends into the oblique fissure (arrow).



A

B

FIG. 3.

(A) Photomicrograph showing pleural thickening, pulmonary fibrosis in subpleural parenchyma, and dystrophic ossification surrounding microliths (arrow). Original magnification × 12.5. (B) Line drawing of (A). F–fibrinous exudate over pleural surface. P–thickened visceral pleura. L–peripheral lung parenchyma showing interstitial fibrosis surrounding microliths. A–aerated lung.

right atrium and ventricle were dilated, but the valves were normal. All other organs, including kidneys, pancreas and parathyroid glands, were normal.

The histological appearances of microlithiasis alveolarum have been described (Spencer, 1985) and our case is typical, showing the characteristic, round, concentrically laminated microliths occupying the majority of alveoli in all sections. Microliths accounted for 28% of the lung parenchymal volume, as estimated morphometrically using a random point counting technique on fixed lung sections. Air spaces formed 32% of the lung volume and the interstitium constituted 40%.

Alveolar microliths had a mean diameter of 190 μm (± 40 μm), which is comparable to that of normal alveoli (maximum diameter 200–250 μm). The parenchyma showed diffuse interstitial fibrosis which was most extensive peripherally. In the subpleural region, fibrosis became confluent and showed foci of dystrophic ossification which surrounded isolated microliths (Fig. 3). The visceral pleura in some areas showed fibrous thickening which extended into the interlobar fissures. In addition, a fibrinous exudate containing sparse mononuclear cells partly covered the pleural surface, consistent with a pleural reaction to pneumothorax (Askin et al, 1977). Thus the soft-tissue attenuation on CT corresponds to fibrosis which is partly parenchymal and partly pleural in origin. Together these fibrotic components measured up to 5 mm in thickness. There was no pleural calcification.

DISCUSSION

The plain radiographic findings in pulmonary alveolar microlithiasis are characterised by widespread, sharply defined nodules of calcific density throughout both lungs. Patients often have no respiratory complaints. Although the disease is initially intra-alveolar, with progression interstitial fibrosis develops and emphysematous bullae may appear. The plain radiographic appearance is largely mirrored by the CT findings. Individual nodules could not be resolved even on 3 mm cuts. This is not surprising, as the size of the nodules ranges from 0.01 mm to 3.0 mm (Fraser & Paré, 1979).

The widespread pleural disease is of interest. Gomez et al (1959) reported pleural thickening of the minor fissure in three out of their four patients. Fraser and Paré (1979) cast doubt on this by suggesting that the pleural shadowing seen on the chest radiograph is due to a heavy concentration of microliths in the subpleural parenchyma rather than disease of the pleura itself. However, we have demonstrated fibrosis of both the visceral pleura and subpleural parenchyma which corresponds to the extensive soft-tissue thickening on the CT sections.

Pleural calcification is not an established feature of pulmonary alveolar microlithiasis and Sosman et al (1957), in their extensive series, have reported calcification to be subpleural rather than pleural. Recently, Winzelberg et al (1984) reported pleural calcification on CT, but no pathological confirmation was available. In our case CT suggested the presence of pleural calcification (Fig. 1D), but this was not confirmed on histological examination. Only subpleural microliths and foci of dystrophic ossification were demonstrated (Fig. 3).

Broncho-alveolar lavage has been used with some success in the management of end-stage alveolar proteinosis. There are no reports in the literature of its use in pulmonary alveolar microlithiasis prior to this patient (Mascie-Taylor et al, 1986). The lack of clinical improvement following lavage was mirrored by the lack of change in the grossly increased lung attenuation measurements as assessed by CT examination.

Acknowledgments

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1986, *The British Journal of Radiology*, *59*, 412–414

Case reports

Psammomatous-like calcification in a Brenner tumour of the ovary

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Radiographic demonstration of psammomatous calcification in the female abdomen is almost invariably associated with an ovarian papillary cystadenoma or papillary cystadenocarcinoma (Lingley, 1942; Castro & Klein, 1962). However, identical calcifications have been reported in an ovarian thecoma (Mecca et al, 1974) and a virilising lipid-cell tumour of the ovary (Scully et al, 1982). Ovarian gonadoblastomas may show a similar pattern of calcification (Seymour et al, 1976). We present what we believe is the first description of typical radiographic psammomatous calcification produced by stromal dystrophic calcification in a benign Brenner tumour of the ovary.

CASE REPORT

A 54-year-old black female presented with a 2–3 month history of weakness, decreased appetite, and 15 pounds weight loss. Pelvic examination revealed a 10–12 cm firm, irregular, left adnexal mass. Ultrasound examination demonstrated a solid mass containing multiple focal, echogenic areas with acoustic shadowing, thought to represent calcifications. A radiograph of the abdomen (Fig. 1) exhibited cloud-like, hazy, granular calcification in the left pelvis, compatible with psammomatous calcification.

At surgery a firm left ovarian tumour was resected. A 2 cm diameter area of gritty calcification was seen in the centre of the tumour. A photograph and radiograph of the specimen are shown in Fig. 2. Microscopically, the tumour was composed of a dense, cellular fibrous stroma, throughout which were scattered multiple well circumscribed nests of epithelial cells with areas of stromal dystrophic calcification (Fig. 3). These findings were consistent with a benign Brenner tumour with extensive calcification.

DISCUSSION

Benign Brenner tumours of the ovary and their rare malignant counterparts account for 2–3% of all ovarian neoplasms (Tutschka & Lauchlan, 1978). The tumours are usually small (less than 2 cm in diameter), but sizes up to 20 cm in diameter have been reported. Microscopic examination shows columns or irregular masses of epithelial cells surrounded by dense fibrous tissue. The epithelial cells resemble uroepithelium and are probably derived by metaplasia from the surface epithelium of the ovary or from the rete ovarii. Stromal calcific deposits are a frequent histological feature and may be abundant enough to cause a gritty sensation on cutting.

Psammoma bodies, also called corpora amylaceae, calcipherites, or microliths, are composed of laminated calcium carbonate. Spherules measure 10–100 μm in diameter. The formation of psammoma bodies is induced intracellularly in neoplastic epithelial cells by the accumulation of hydroxyapatite crystals. Large extracellular psammoma bodies result from fused calcific bodies which have been extruded from calcified cells and are thought to be a consequence of ischaemia and resulting cellular degeneration (Sorbe & Frankendal, 1982). Tumours most commonly containing psammoma bodies are meningiomas, medullary carcinoma of the thyroid, and papillary serous ovarian neoplasms (Tutschka & Lauchlan, 1978).

The radiological appearance of psammoma bodies depends on the size of the neoplastic mass and the concentration of calcifications. The density is less than that of most calcifying masses and usually appears as a hazy, cloud-like aggregation only slightly more dense

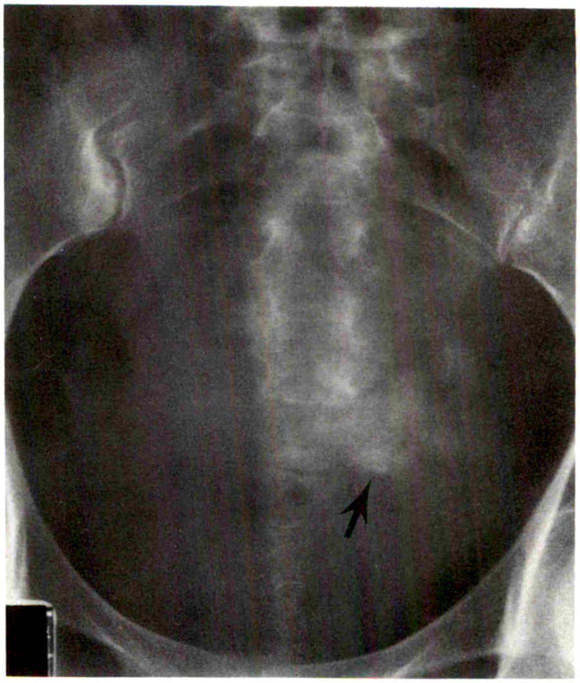

FIG. 1.

Plain radiograph of the pelvis showing psammomatous-like calcifications (arrow).

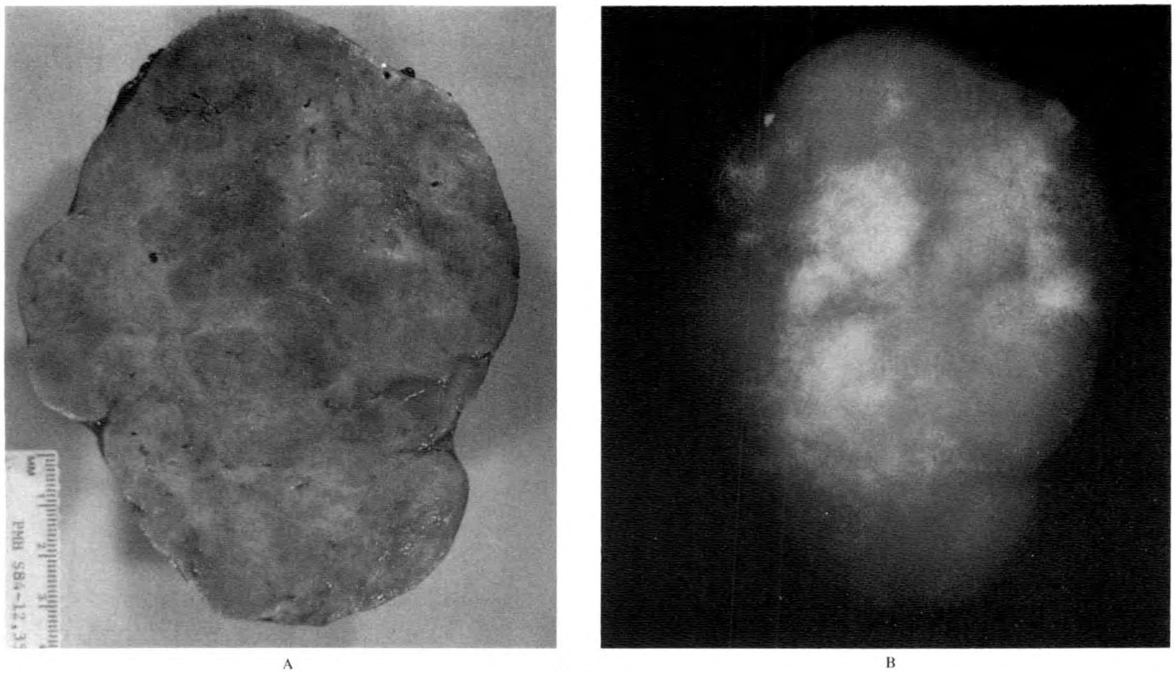

FIG. 2.

Gross specimen (A) and radiograph of specimen (B) showing diffuse dystrophic calcifications.

than soft tissue. The presence of true psammomatous calcification in the abdomen of a woman may be considered pathognomonic of ovarian papillary serous cystadenoma or papillary serous cystadenocarcinoma. It is unfortunate that some rare ovarian tumours, such as the Brenner tumour, thecoma, virilising lipid-cell tumour and gonadoblastoma, may contain dystrophic calcification that mimics true psammomatous calcification.

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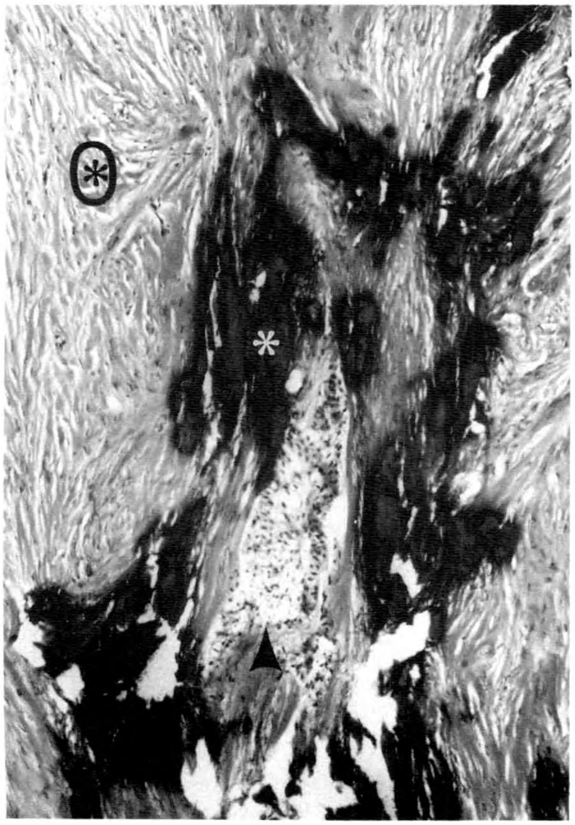

FIG. 3.

Photomicrograph of specimen demonstrating fibrous stroma (circled black asterisk), dystrophic calcification (white asterisk), and a nest of epithelial cells (arrowhead).

1986, *The British Journal of Radiology*, *59*, 414–416

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Intracranial Hodgkin's disease

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Intracranial deposits are rare in Hodgkin's disease. When this complication does occur, it is usually seen in patients who have relapsed with widespread disease. We report two patients with Hodgkin's disease who developed cerebral deposits. In one patient it was a terminal event. In the other it was apparently the only site of relapse.

CASE REPORTS

Case 1

A man aged 22 years presented in January 1979 with a 3-year history of an enlarged gland in the right axilla. He had no "B" symptoms. On examination he had enlarged nodes in the right axilla and on both sides of the neck. A chest radiograph showed no abnormality. Biopsy of an axillary node showed nodular sclerosing Hodgkin's disease. A lymphogram was normal but at staging laparotomy he was found to have involvement of a coeliac node and of the spleen. The final pathological staging was IIIAs.

Chemotherapy using the MOPP regime was started, but after completing three cycles he was not in remission, so it was decided to use radiotherapy in addition. Treatment to the cervical, axillary, mediastinal and upper para-aortic nodes was given using the "mantle" technique. He received a dose of 3800 cGy in 16 fractions over a period of 4 weeks to these areas. Chemotherapy using MOPP was continued after this treatment. By June 1979 he had received a further three cycles, but he now had evidence of intra-abdominal lymphadenopathy and an isolated deposit in the left lobe of the liver. Further radiotherapy was given to the involved areas.

In September 1979 the patient was found to have enlarged inguinal nodes which were irradiated. Two months later he developed pain in the back. Radiographs showed involvement of the 6th and 7th thoracic vertebrae. After palliative radiotherapy to the affected vertebrae he was maintained on cyclophosphamide, vinblastine and prednisolone. This seemed to slow the progress of his disease until August 1980 when he was found to have recurrent cervical nodes.

In December 1980 he had three episodes of Jacksonian epilepsy. A CT scan showed a low-attenuation lesion in the posterior part of the right frontal lobe which enhanced with contrast medium (Figs 1 and 2). Craniotomy and biopsy confirmed Hodgkin's disease. He did not recover from the operation and died a few days later from bronchopneumonia. Post-mortem examination showed widespread Hodgkin's disease involving cervical, inguinal and iliac nodes, lungs, liver, kidney and bone.

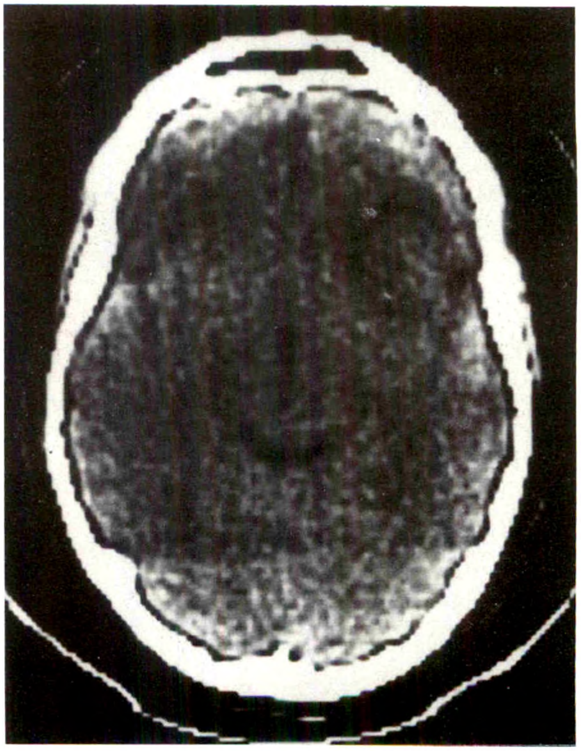

FIG. 1. *Case 1.*

Unenhanced CT scan showing a low-attenuation lesion in the right frontal lobe (L + 32, W 75).

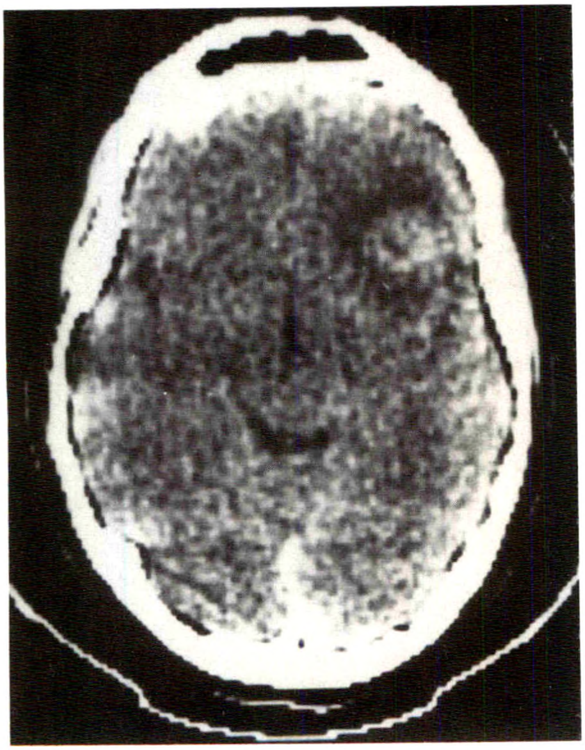

FIG. 2. *Case 1.*

Enhancement of the lesion following injection of intravenous contrast medium (L+32, W 75).

Case 2

A woman aged 25 years presented in February 1981 with an enlarged gland on the right side of the neck. She gave a history of fever and of night sweats and she had lost a significant amount of weight. On examination she was found to have enlarged nodes on both sides of the neck, in the right infraclavicular region and in the right axilla. A chest radiograph showed enlarged paratracheal and hilar nodes. Biopsy of a cervical node showed nodular sclerosing Hodgkin's disease. A lymphogram and a CT scan showed no evidence of disease below the diaphragm. Factors indicating a poor prognosis were a Hb level of 9.1 g/dl, an ESR of 150 mm in 1 h and an alkaline phosphatase of level 151 IU/l. She was considered to have Stage IIB disease.

Chemotherapy using the MOPP regime was started in April 1981. She was in remission after two cycles but, haematologically, she tolerated the treatment poorly and became pancytopenic in September 1981. Whilst recovering from this complication she was found to have recurrent disease in the right infraclavicular fossa. She was given radiotherapy to all node areas above the diaphragm using the "mantle" technique, receiving a dose of 3800 cGy in 16 fractions over a period of 4 weeks. She was in remission after this treatment and remained well until September 1982 when she developed herpes zoster on the left side of her neck; this became disseminated and necessitated her admission to hospital.

The herpetic lesions were very slow in resolving and it was not until April 1983 that the ulcers finally healed. By this time there was evidence of recurrence of the Hodgkin's disease with night sweats, a raised ESR and an abnormal Ga scan. Chemotherapy consisting of chlorambucil, vinblastine, procarbazine and prednisolone was started. By September 1983 she had received five cycles, which were again tolerated poorly from the haematological point of view and the treatment was discontinued, partly at her own request.

In February 1985 she developed nausea and vertigo. On examination she had nystagmus on looking to the left, but no other neurological abnormality and no evidence of disease elsewhere. A CT scan of the brain showed a low-density lesion in the left cerebellar hemisphere and another in the right frontal lobe, neither of which showed enhancement with contrast medium (Fig. 3). As the findings were consistent with Hodgkin's disease it was decided to forego a tissue diagnosis in this patient. She was given cranial irradiation under steroid cover, receiving a dose of 3500 cGy in 16 fractions over a period of 4 weeks. She made a full clinical recovery and a CT scan done 2 weeks after she had completed her treatment showed complete resolution of the lesions (Fig. 4).

DISCUSSION

An estimate of the rarity of intracranial Hodgkin's disease may be made from the paucity of such cases reported in the literature. The most recent review is that of Saposnik and Kaplan (1983) who collected 30 reported cases and added 12 of their own. Although certain risk factors were postulated in some of the earlier reports such factors could not be identified in the larger series.

The first well documented case of intracranial Hodgkin's disease, confirmed histologically, was reported by Fein and Newill (1954). At that time the prognosis of advanced Hodgkin's disease was poor, with a 5-year survival rate of about 20% (Kaplan,

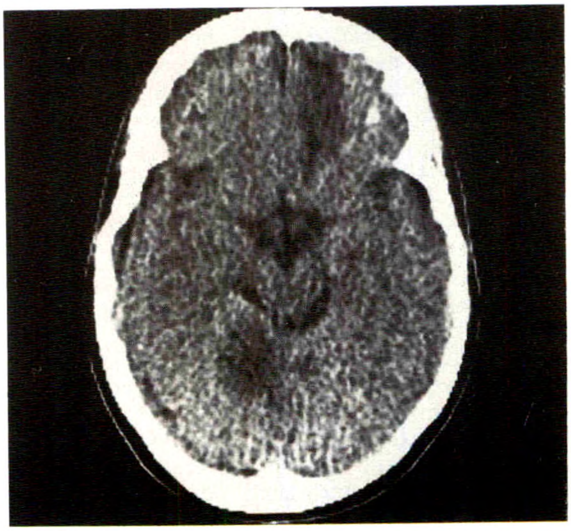

FIG. 3. *Case 2.*

Unenhanced CT scan showing low-attenuation areas in the left cerebellar hemisphere and in the right frontal lobe (L+24, W 64).

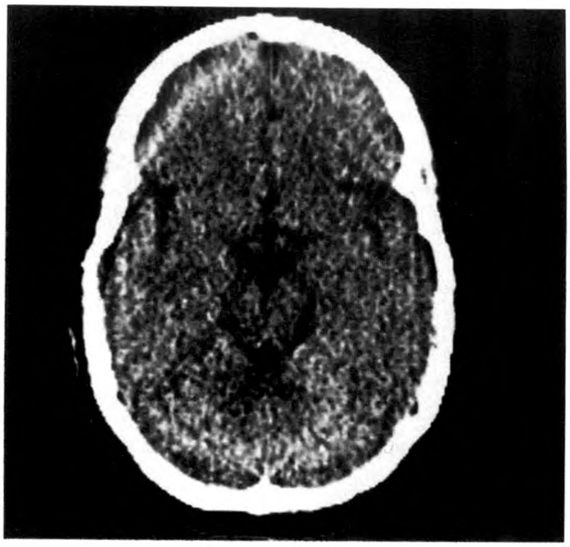

FIG. 4. *Case 2.*

A repeat CT scan 6 weeks later showing no obvious abnormality (L + 24, W 64).

1980). The introduction of combination chemotherapy (De Vita et al, 1970) improved prognosis considerably, and a complete remission rate of 80% can now be achieved in Stage III and Stage IV disease. This improvement in long-term survival in patients with advanced disease may partly explain the increased number of reported cases of intracranial Hodgkin's disease. The situation may be analogous to the increased incidence of leukaemic meningitis in acute lymphatic leukaemia. Before the introduction of effective chemotherapy for this condition patients seldom lived long enough for involvement of the central nervous system to manifest itself.

It had previously been suggested that intracranial disease occurred by direct spread from the bones of the skull or in continuity with meningeal or dural deposits, having gained access to the skull via the cranial nerves. Sapoznik and Kaplan (1983) concluded, however, after analysing concurrent sites of disease, that this was not always the case and that haematogenous spread was probably the commonest mechanism.

Intracranial Hodgkin's disease, in the absence of disease elsewhere in the body, appears to be very rare. In the earlier series of Cuttner et al (1979), 21 of 23 patients had disease elsewhere in the body at the time they were found to have involvement of the central nervous system. Only two out of 12 patients in another series (Sapoznik & Kaplan, 1983) had intracranial disease without having disease at another site.

The appearance of intracranial lymphoma on CT scanning can vary widely. There may be infiltrating, low-attenuation lesions that show little or no enhancement, or deposits that appear as hyperdense, strongly enhancing lesions with surrounding oedema. As some of these features can be seen with localised fungal infections of the brain, biopsy may be deemed necessary to make a diagnosis. Cytological examination of the cerebrospinal fluid is seldom helpful in these patients and lumbar puncture is best avoided because raised intracranial pressure may be a feature of this condition.

Sapoznik and Kaplan (1983) stress that intracranial Hodgkin's disease should be treated with intent to cure, especially if disease elsewhere is absent or amenable to curative treatment. Although intracranial relapse carries a worse prognosis than relapse at other sites, the results of radiotherapy to the whole brain, giving a dose of 2000 cGy followed by a supplementary dose of 2000–3000 cGy to the tumour area, show an improvement in median survival from a historical median of 2 months to one of 10 months.

Both the patients reported here had nodular sclerosing Hodgkin's disease. The first patient responded poorly to radiotherapy and, in fact, developed recurrent disease within a previously irradiated area. He also responded poorly to chemotherapy although it undoubtedly held the disease in check for a time, and thus prolonged his life. The occurrence of intracranial disease marked the end-stage of a relentless 2-year progression and proved to be fatal. The second patient is more unusual in that the intracranial disease revealed itself after she had apparently been in remission for 2 years, and it appeared to be the only site of relapse. The condition responded rapidly to radiotherapy and she remains well, with no sign of disease in the central nervous system or elsewhere, 6 months after completing her course of radiotherapy.

The occurrence of intracranial Hodgkin's disease is now well documented and we report two additional cases. It is important to recognise that this complication can occur in patients who are apparently in remission.

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1986, *The British Journal of Radiology*, *59*, 417–418 APRIL 1986

Case of the month

Haematuria: a red herring?

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A previously fit 21-year-old male was admitted with a recent history of lethargy, malaise, sore throat, dark urine and rigors. Haematuria and proteinuria had been noted by his general practitioner. A more detailed history on admission revealed that his sister had previously been investigated for a pulmonary abnormality. There was no abnormality on physical examination. Haematuria and proteinuria were confirmed on "stix" testing and urine microscopy showed red cells and red cell casts. Haematological, biochemical, and bacteriological tests, including erythrocyte sedimentation rate (ESR), antistreptolysin titres, complement, immunoglobulins, creatinine clearance and numerous blood cultures, were normal. A chest radiograph on admission was considered normal (Fig. 1).

Following admission, his clinical condition and renal function remained stable, yet his haematuria and proteinuria persisted. An intravenous urogram (IVU) was performed (Fig. 2).

What is the abnormality and

What clinical history should be sought?

What is the diagnosis?

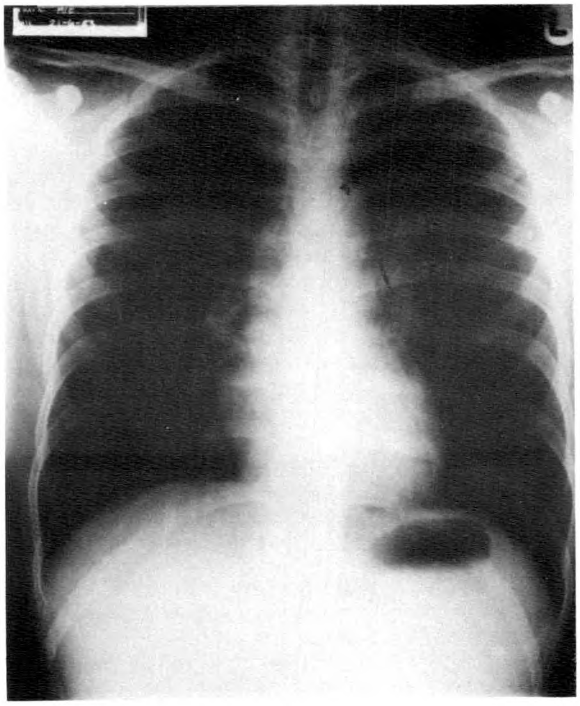

FIG. 1.

Chest radiograph on admission.

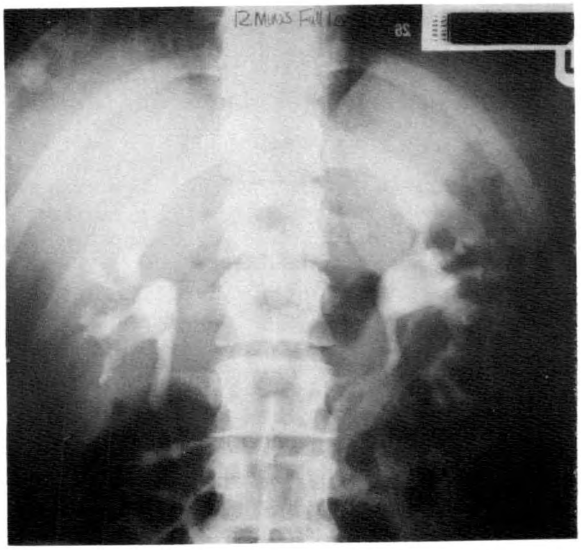

FIG. 2.

Full-length IVU.

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The IVU is normal apart from a well defined lobulated opacity at the right lung base with feeding vessels: an arterio-venous malformation (AVM). Review of the chest radiograph confirmed this lesion and showed similar lesions at both bases.

In the light of these findings, specific enquiry revealed that the patient had suffered numerous epistaxes during childhood, as had his father and sister. The latter, in addition to abnormalities on her chest radiograph, had red spots on her lips. A more detailed examination of our patient revealed bilateral basal bruits and a few small buccal telangiectases.

Hereditary haemorrhagic telangiectasia (HHT) with pulmonary arteriovenous malformations was diagnosed.

Subsequently, his clinical condition deteriorated, with an intermittent pyrexia and rising white cell count (WCC) and ESR. Haematuria and proteinuria persisted.

Although urine microscopy indicated a glomerular site for his haematuria, renal vascular malformations were excluded by selective renal arteriography. Cystoscopy showed only a small telangiectasis on the bladder mucosa. The number, size and site of the AVMs were defined by pulmonary angiography, there being three at the right base and one at the left base (Fig. 3).

Renal biopsy was the definitive investigation in this case and showed chronic interstitial nephritis and mesangial proliferative glomerulonephritis. Immunofluorescent and electron microscopic changes were compatible with immune-complex deposition. It was thought that an AVM had become infected, giving rise to a low-grade septicaemia and immune-complex formation resulting in a glomerulonephritis. Since antibiotics produced no improvement, the AVMs were excised at bilateral thoracotomy. Although his pyrexia subsequently resolved, the resected specimens showed no evidence of infection. Six months after presentation he remains well with normal ESR and WCC, but his haematuria and proteinuria persist.

DISCUSSION

Hereditary haemorrhagic telangiectasia is an autosomal dominant condition with variable penetrance, characterised by mucocutaneous and systemic vascular abnormalities. It was first reported in 1864 when a case of hereditary epistaxis was described (Sutton, 1864). Subsequently, many authors have described other aspects of the condition, resulting in the eponymous title of Osler–Rendue–Weber syndrome.

The telangiectases typically present in the second and third decades, recurrent epistaxis being by far the most common manifestation. Pulmonary AVMs are a common feature of HHT and are present in 10–15% of cases (Graff, 1983). They are abnormal communications between a single artery and a draining vein without any intervening capillary circulation. Only 40% present with symptoms, usually dyspnoea or recurrent haemoptysis. Finger clubbing, arterial bruits, cyanosis and polycythaemia are the usual clinical signs (Dines et al, 1974). Fifty to sixty per cent of pulmonary AVMs occur in association with HHT, this being more likely when the AVMs are multiple. This association is of clinical relevance since symptoms progress more rapidly and the incidence of complications, such as cerebral abscess, is higher when pulmonary AVMs and HHT coexist (Graff, 1983).

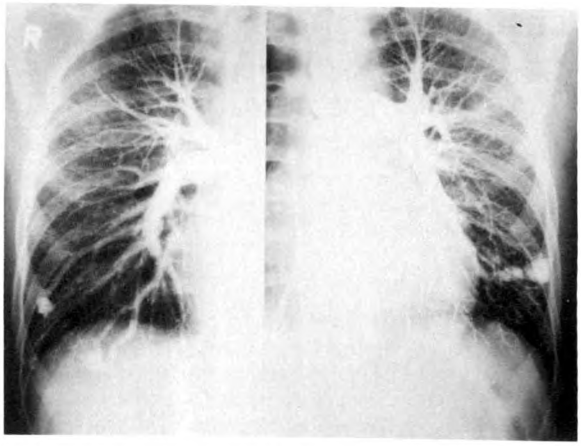

FIG. 3.

Composite pulmonary angiogram.

Surgical excision has been the standard method of treatment for AVMs but, recently, detachable balloon catheter embolisation has been described (White et al, 1980). As there is only a single feeding artery, this technique appears promising. Controlled trials have failed to show benefit from systemic oestrogen therapy.

In the present case, HHT coexists with a proliferative glomerulonephritis and renal immune complex deposition. So far as we know, this association has not been described previously. It seems unlikely that they are causally related, since the haematuria and proteinuria persist after removal of the AVMs, which were found not to be infected. Although immune complex disease is not described with AVMs/HHT, recently it has been found that a chronic form of disseminated intravascular coagulation (DIC) occurs in over 50% of cases of HHT (Bick, 1981). While rather speculative, it may be that the same vascular insult required to promote chronic DIC could result in immune-complex formation and subsequent renal deposition.

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Short communications

3D positron emission tomography: preliminary results

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(Received October 1985)

Quantitative radionuclide imaging has been a principal objective of most groups working with emission tomography. Positron emission tomography (PET) has been shown to be capable of providing quantitative images (Beller et al, 1982; Bergstrom et al, 1983, Beaney, 1984) which have contributed much to the understanding of cerebral and myocardial disease. Recently we have shown how a low cost prototype multiwire proportional chamber (MWPC) positron camera can produce longitudinal tomograms from limited-angle data acquisition via large area detectors (Ott et al, 1983; Flower et al, 1984) These tomograms were essentially qualitative in nature but provided enhanced image contrast when compared with conventional planar scintigraphy.

In this paper we describe preliminary results of multiprojection acquisitions performed with the same detector providing 3D volume images. These images are intrinsically quantitative in nature and provide high-resolution, multiple-slice tomograms of the object being imaged Two examples of the clinical utilisation of these quantitative measurements of the uptake of radiopharmaceuticals *in vivo* are briefly described

MATERIALS AND METHODS

The prototype MWPC positron camera has been extensively described elsewhere (Bateman et al, 1984) In previous studies, images were obtained without detector rotation because the design of this prototype precluded such motion. In order to obtain multiview acquisitions, a special chair was designed to enable patients or phantoms to be rotated within the field of view of the camera Positron emission tomographic imaging was carried out with a range of radiopharmaceuticals labelled with either a long-lived radionuclide, ^{124}I, or with ^{68}Ga from an ionic ^{68}Ge/^{68}Ga generator Two studies illustrate the improved imaging and quantitative potential of this system.

The first was the measurement of the functional volume of the thyroid and uptake of radioiodine in the thyroid of patients suffering from thyrotoxicosis Accurate measurement of the radiation dose to the thyroid following radioiodine therapy has always been difficult because estimation of the functional thyroid volume is difficult and the intrathyroid distribution of the radionuclide has not been known. This study used Na^{124}I (Akbari et al, 1985) given orally, imaging and uptake measurements were performed 24 h after administration. Most patients received a mixed drink of 55 MBq of ^{131}I and 25 MBq of ^{124}I.

The second demonstration of the utility of the system involved the use of ^{68}Ga-EDTA to study blood–brain barrier breakdown in patients with cerebral lesions, in particular to relate this to future measurements of tumour viability after therapy

In all cases, data acquisition consisted of eight contiguous views of the patient covering a 180° rotation, with each view covering a 22.5° sector The acquisition was performed by taking the first four views (1,3,5,7) in the clockwise direction and the second four views (8,6,4,2) anticlockwise, to average out temporal variations during the study The average acquisition time per view was about 2–3 min, the number of events per study was typically 400 000 for thyroid imaging, and between 250 000 and 500 000 for blood–brain barrier imaging

Each multiview data acquisition was stored on magnetic tape and subsequently analysed on a VAX 11/750 computer. The data were back-projected into a $64 \times 64 \times 64$ volume matrix and images were reconstructed using a technique (Clack et al, 1984) to deconvolve the 3D point-source response function. The deconvolution was combined with a spatial frequency smoothing function to minimise image noise artefacts. The images were then displayed as transaxial, sagittal, and coronal sections of the object. For thyroid studies, voxel sizes were $(3 \times 3 \times 3)$ mm^3, giving an image volume of about $(20 \times 20 \times 20)$ cm^3. For the brain studies, voxel sizes were chosen as $(5 \times 5 \times 5)$ mm^3, giving an image volume of about $(30 \times 30 \times 30)$ cm^3. Hence, in these studies the slice thickness in each direction was 3 mm or 5 mm and there were no interslice gaps.

Finally, it was possible to produce 3D volume images of the object by using shaded contour display software (Brigham Young University, 1984). This allowed the 3D outline of the object to be displayed from any orientation Further computer software allowed these 3D images to be rotated to provide a video display of the functional volume

PRELIMINARY RESULTS AND DISCUSSION

^{124}I thyroid imaging

A selection of patient studies is shown in Figs 1–4. The photons from the ^{131}I in the mixture gave rise to a random rate of 20–40%, which was acceptable with these detectors. These images illustrate the potential of the small prototype detectors

Figure 1A shows a planar thyroid image taken with an HP37 gamma camera/pinhole collimator combination and Fig. 1B shows four 3 mm thick coronal PET slices of the same patient (Case 1) suffering from Graves' disease All images show the radionuclide distribution to be uniform

A planar thyroid image of another patient (Case 2), apparently suffering from Graves' disease, is shown in Fig. 2A together with associated 3 mm thick coronal PET slices (Fig. 2B) The tomographic images show a non-uniformity in the distribution of the radionuclide in distinct contrast to the conventional planar image This indicates that measurements

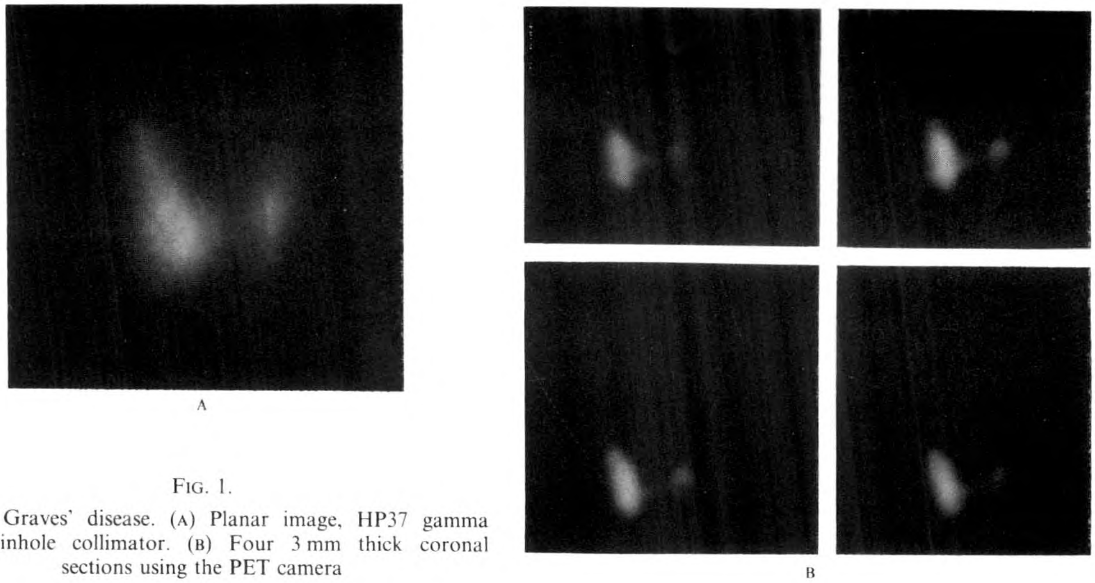

FIG. 1.
Case 1. Graves' disease. (A) Planar image, HP37 gamma camera/pinhole collimator. (B) Four 3 mm thick coronal sections using the PET camera

of radiation dose to the thyroid on the assumption of the uniform distribution as seen by planar scintigraphy are grossly in error.

Figure 3 shows a planar thyroid image of a patient (Case 3) with Graves' disease and associated coronal/transaxial/sagittal PET slices. The pyramidal lobe, crudely shown in the conventional image (Fig. 3A) is clearly delineated by the tomographic technique (Fig. 3B–D). This lobe lies anteriorly to the normal right lobe. The images confirm the detail which can be shown with a high resolution detector.

Shaded contour images constructed from the 3D data sets of this patient are shown in Fig. 4. It is possible to view the surface of the thyroid from any orientation and to make the surface transparent to show internal structure. These images show clearly the functional structure of the thyroid and enable the physical size of regions of increased radionuclide uptake to be determined. This technique demonstrates a new method of showing organ detail, and it should be equally valuable in the imaging of other organs. Figure 4B views the thyroid from above and shows clearly how the two lobes of the thyroid curve around the trachea.

These data show already the visual improvement in information content relating to the radiopharmaceutical distribution and radiation dosimetry. The study is being

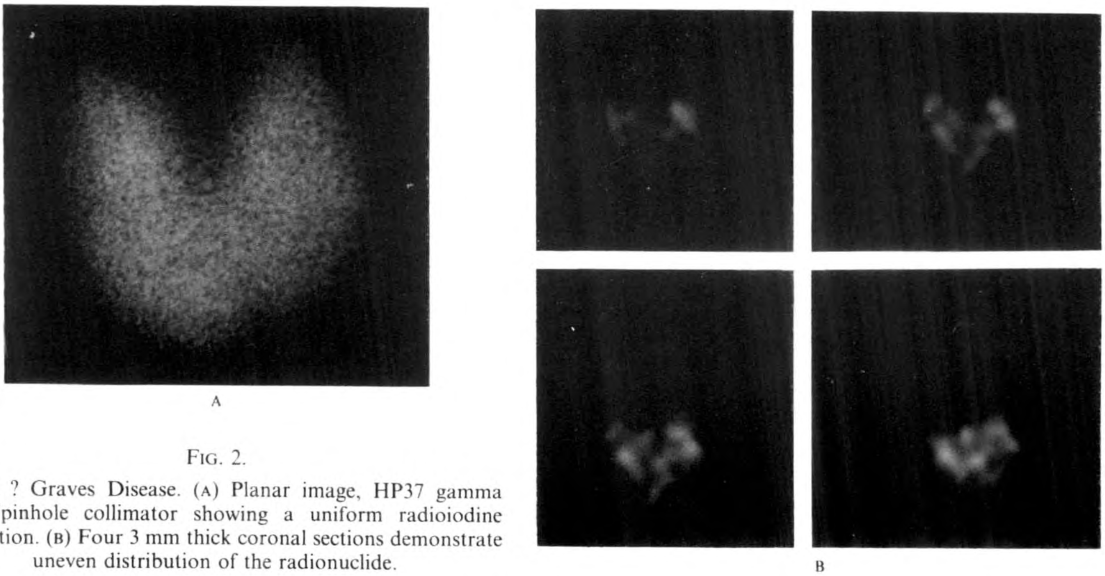

FIG. 2.
Case 2. ? Graves Disease. (A) Planar image, HP37 gamma camera/pinhole collimator showing a uniform radioiodine distribution. (B) Four 3 mm thick coronal sections demonstrate uneven distribution of the radionuclide.

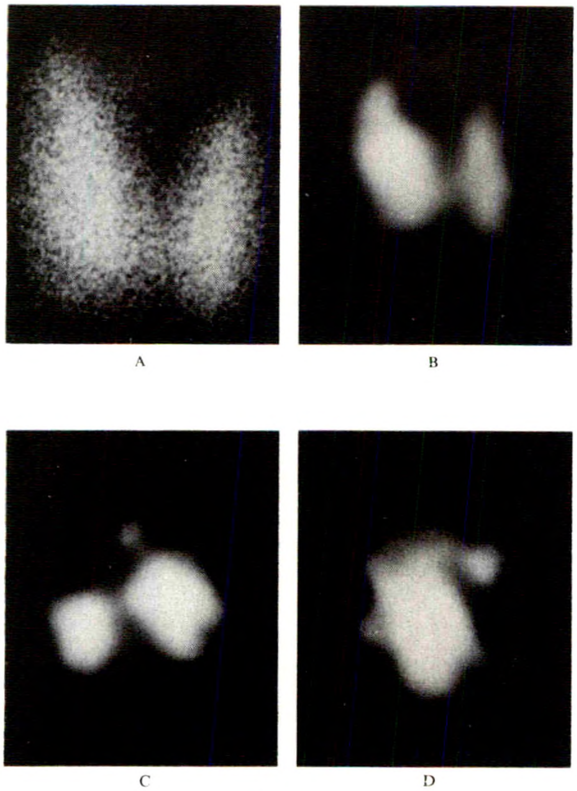

FIG. 3.

Case 3. Graves' disease. (A) Planar image, HP37 gamma camera/pinhole collimator. (B) Coronal, (C) transaxial and (D) sagittal 3 mm thick PET sections demonstrate anteriorly placed small pyramidal lobe.

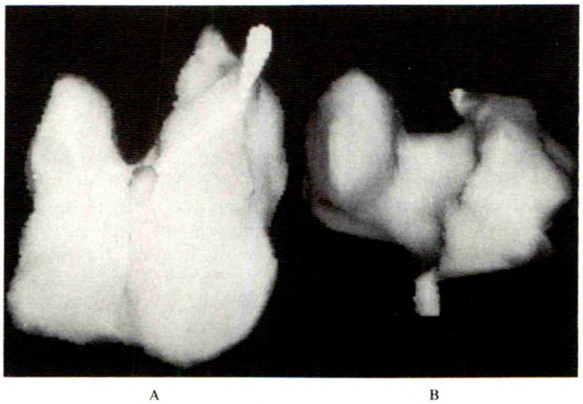

FIG. 4.

Case 3. 3D shaded counter images: (A) anterior view, (B) superior view. Note the moulding of the thyroid around the trachea.

extended to determine the accuracy that can be obtained in the measurement of functional volume (Ott et al, 1985a; Webb et al, 1985).

^{68}Ga-EDTA brain imaging

Figure 5 shows four 5 mm thick transaxial slices of a normal-brain study (Case 4), obtained with a small injected dose of 80 MBq of ^{68}Ga-EDTA. The quality of the images is clearly comparable to that obtained by other PET detectors. The method of patient positioning for data acquisition using the rotating chair is at present very unsatisfactory for these studies and the full imaging potential of the device is unlikely to be achieved because of patient/chair movement during the study. It is unlikely that the image quality will improve without much better patient immobilisation, but the preliminary studies confirm the ability to obtain good brain images with a ^{68}Ga labelled pharmaceutical.

Future developments

The thyroid imaging study is now being extended to the measurement of total thyroid and intrathyroid radiation doses from radioiodine therapy. The high spatial resolution and sensitivity achieved in PET has enabled the functional volume of the thyroid to be measured to an accuracy better than 10% (Ott et al, 1985b) and will provide quantitative information to relate radiation dose measurements to clinical results. This same technique will be used to provide quantitative measurements of radiopharmaceutical uptake, such as MIBG in metastatic disease in other parts of the body, information which may prove useful in calculating the appropriate therapy doses.

A larger-area clinical positron camera is now under construction. This new detector will be attached to a rotating gantry and will provide a spatial resolution of less than 5 mm and, ultimately, a sensitivity of about 10 times that of the

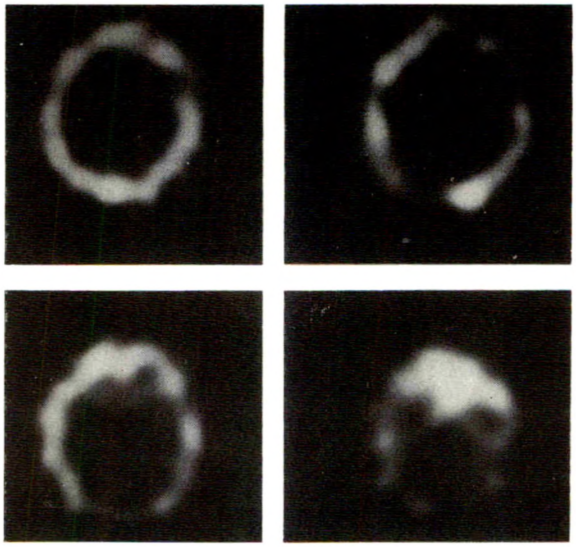

FIG. 5.

Case 4. Normal brain scan taken 10 min following intravenous injection of 50 MBq of ^{68}Ga-EDTA: 5 mm thick transaxial sections separated by 10 mm.

present prototype (Marsden et al, 1985) This MWPC PET camera is being manufactured for little more than the cost of a modern gamma camera head and should, ultimately, have a sensitivity approaching that of present state-of-the-art multicrystal PET detectors (Litton et al, 1984)

The future utilisation of these positron camera systems will continue to be carried out without the need for an on-site cyclotron Simple techniques for the production of ^{68}Ga-labelled radiopharmaceuticals are being developed to provide agents usable in a routine nuclear medicine department. This, in addition to the use of reasonably long-lived positron-emitting radionuclides such as ^{18}F, ^{52}Fe, ^{55}Co and ^{124}I, will provide a flexible, low-cost PET imaging system for nuclear medicine.

CONCLUSIONS

These preliminary studies confirm the feasibility of performing positron emission tomography with a low cost detector remote from a cyclotron, to provide clinically useful quantitative information related to the therapy of primary and metastatic disease.

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Short communications

A Phase I study of the combined hypoxic cell radiosensitisers, Ro 03-8799 and SR 2508: a preliminary report of single-dose toxicity, pharmacokinetics and tumour concentrations

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Two hypoxic cell radiosensitisers currently being evaluated are the misonidazole analogues Ro 03-8799 and SR 2508. An acute central nervous system syndrome limits single doses of Ro 03-8799 to 0.75 g/m² (Roberts et al, 1984, Saunders et al, 1984; Roberts et al, 1986). Peripheral neuropathy limits the total dose of SR 2508 to 30 g/m², but individual doses of ⩾ 3 g/m² are tolerable (Coleman et al, 1984). As the hydrophilic SR 2508 is largely excluded from the brain (Brown & Workman, 1980) and Ro 03-8799 does not cause peripheral neuropathy (Roberts et al, 1984; Saunders et al, 1984, Roberts et al, 1986), it may be possible to combine these drugs to therapeutic advantage without increased toxicity.

Ethical committee and patient informed consent was obtained to conduct a Phase I study to determine a safe single dose of SR 2508 which may be combined with 0.75 g/m² of Ro 03-8799. We report the preliminary results in this short communication. Ro 03-8799 (hydrochloride salt) was provided by Roche Products Limited, Welwyn, UK and SR 2508 by the US National Cancer Institute.

The drugs were given together by intravenous infusion in 50 ml saline over 10 min. Two patients were treated at each of five escalating dose levels, beginning at 0.5 g/m² of each drug, and proceeding to a fixed dose of 0.75 g/m² of Ro 03-8799 with escalating doses of SR 2508 at 0.5, 1, 2 and 3 g/m². No immediate side-effects were seen in the two patients receiving 0.5 g/m² of each drug. At 0.75 g/m² of Ro 03-8799 (with 0.5–3 g/m² SR 2508) four out of eight patients experienced sweating and one patient experienced a feeling of mental detachment. This incidence did not appear to be related to the accompanying dose of SR 2508 and was similar to that expected for 0.75 g/m² of Ro 03-8799 alone (Roberts et al, 1984; Saunders et al, 1984, Roberts et al, 1986). No peripheral neuropathy has been seen after a minimum follow-up time of 6 weeks.

Blood samples were taken for a minimum plasma time course of 24 h in all 10 patients, and 24 h urine collections were obtained from nine of them. Concentrations of Ro 03-8799, its N-oxide metabolite and SR 2508 were determined by reversed-phase high-performance liquid chromatography (HPLC) using published methods (Workman et al, 1978, Malcolm et al, 1983) with minor modifications. For Ro 03-8799 both drug doses and concentrations refer to the hydrochloride salt.

Plasma pharmacokinetics and urinary recoveries were very similar to those reported for each agent alone (Roberts et al, 1984; Coleman et al, 1984; Saunders et al, 1984, Roberts et al, 1986), indicating no major drug interaction. For the 10 patients in the Phase I study, mean plasma elimination half-life values (±SD) were almost identical at 5.45 (±1.09) h and 5.33 (±1.10) h for Ro 03-8799 and SR 2508, respectively, these values being independent of dose. Plasma concentrations at early times after the end of infusion are summarised in Table I. Concentrations declined with time and were proportional to dose, bearing in mind the small numbers per dose escalation. The mean 24 h urinary recovery (±SD) was 37 (±15)% for Ro 03-8799 and 62(±16)% for SR 2508.

Sequential tumour biopsies were obtained in three of the Phase I patients and in an additional two patients administered 0.5 g/m² of each drug, giving a total of five patients in all. Of these, one patient had breast cancer and the remainder had superficial metastases from melanoma (two), small-cell lung cancer (one) and adenocarcinoma of uncertain origin (one). Table II gives details of tumour concentrations for three patients. In agreement with the results for the two sensitisers given independently (Coleman et al, 1984; Roberts et al, 1984, Saunders et al, 1984; Roberts et al, 1986), Ro 03-8799 is concentrated two- to sevenfold in tumour, while SR 2508 reaches 40–100% of the corresponding plasma level but

TABLE I

PLASMA CONCENTRATIONS AT EARLY TIMES AFTER THE END OF INFUSION FOR THE 10 PATIENTS IN THE PHASE I STUDY

Drug	Dose (g/m²)	Number of patients	Mean plasma concentration (μg/ml)			
			0 min	15 min	30 min	60 min
Ro 03-8799	0.5	2	15.5	8.4	7.0	5.8
Ro 03-8799	0.75	8	21.0	12.0	9.7	8.4
SR 2508	0.5	4	60.3	28.1	23.3	19.0
SR 2508	1.0	2	94.9	44.5	38.4	28.1
SR 2508	2.0	2	162.3	113.8	99.5	69.3
SR 2508	3.0	2	306.7	172.6	131.0	100.1

TABLE II

CONCENTRATIONS OF RO 03-8799 AND SR 2508 IN PLASMA AND TUMOUR BIOPSIES

Time (min) from end of 10 min infusion	Ro 03-8799 (μg/g)			SR 2508 (μg/g)		
	Plasma (P)	Tumour (T)	T/P (%)	Plasma (P)	Tumour (T)	T/P (%)
(A) *Malignant melanoma receiving 0.75 g/m² Ro 03-8799 with 2 g/m² SR 2508*						
0	15.3	17.0	111	165	73	44
5	10.0	25.4	254	162	70	43
10	8.3	7.3	88	135	44	33
15	8.1	17.6	217	111	72	65
30	6.0	25.7	428	98	71	73
(B) *Malignant melanoma receiving 0.75 g/m² Ro 03-8799 with 1 g/m² SR 2508*						
0	17.1	75.8	468	105	42.8	41
5	14.0	71.6	512	75.1	67.3	90
10	11.7	76.2	652	57.8	25.1	43
15	11.3	82.2	724	53.9	41.0	76
30	10.2	73.6	752	39.9	41.3	104
60	10.1	65.9	652	32.3	27.6	85
(C) *Adenocarcinoma of uncertain origin receiving 0.5 g/m² Ro 03-8799 with 0.5 g/m² SR 2508*						
0	4.1	16.4	395	20.4	14.1	69
5	5.9	11.4	192	38.2	13.4	35
10	5.2	16.4	313	33.3	15.8	47
15	5.4	26.6	488	29.3	19.6	67
30	6.1	19.4	320	25.7	17.7	69
45	5.9	25.6	434	23.0	13.4	58

achieves higher absolute levels. Concentrations of both drugs were fairly constant up to 30 min, and previous studies have recommended 20–30 min as the optimal time for radiotherapy (Coleman et al, 1984; Roberts et al, 1984; Saunders et al, 1984; Roberts et al, 1986). Normalising to a dose of 0.75 g/m² Ro 03-8799 and 2 g/m² SR 2508, the average tumour concentrations (±2 SE) for the five patients over the period 0–30 min were 29.5 (±10.6, $n = 24$) μg/g for Ro 03-8799 and 62.8 (±11.1, $n = 24$) μg/g for SR 2508. Comparing these with data for the sensitisers given alone, the SR 2508 figure is close to that of 76 μg/g calculated from the data of Coleman et al (1984) while the value for Ro 03-8799 is slightly lower than that of 47 μg/g (Roberts et al, 1984, 1986) and 58 μg/g (Saunders et al, 1984) in two much larger series.

There is known to be considerable variation between patients (Roberts et al, 1984; Saunders et al, 1984; Roberts et al, 1986). A previous study suggested that the tumour/plasma ratio is reduced in samples containing a low proportion of viable tumour as assessed histologically (Saunders et al, 1984). An estimate of tumour necrosis and fibrosis was, therefore, made. Within the limits of sampling error, there was no significant variation in sensitiser concentrations between samples judged to be totally viable and those containing extensive areas of necrosis or fibrosis. For example, for Patient A, all the samples showed a high proportion of viable tumour including the 10 min sample giving a comparatively low value. For Patient B, the 15 min sample showed extensive necrosis, but exhibited sensitiser concentrations similar to the other biopsies which were mainly viable. These are obviously early results and the slightly low figure for Ro 03-8799 compared with previous work is probably a result of the small numbers. Additional patients are now being studied.

For the purpose of predicting the potential effectiveness of the combined radiosensitisers, we have based the calculations on the achievement of tumour concentrations of 70 μg/g with 2 g/m² SR 2508 and either 30 μg/g Ro 03-8799 (present study) or 50 μg/g (earlier studies) with 0.75 g/m² Ro 03-8799. On the basis of SR 2508 having equivalent radiosensitisation efficiency to misonidazole (Brown et al, 1981), while Ro 03-8799 is approximately 2.5 times more potent (data from Smithen et al, 1980; Dennis et al, 1985), the combined radiosensitisers give concentrations equivalent to between 119 and 153 μg/g (0.59–0.76 mM) misonidazole. This represents an improvement of 3.7–4.8-fold over the concentration of about 32 μg/g (0.16 mM) which can be obtained with 1 g/m² misonidazole (Roberts et al, 1986). Precise estimations of enhancement ratios are difficult because of differences in cell lines and other variables. However, based on the widely used Gray Laboratory data for hypoxic V79 cells *in vitro* (Williams et al, 1982) and correcting for intracellular concentrations (Dennis et al, 1985), this combination of sensitisers would be expected to give a single dose enhancement ratio of 1.5–1.6. These compare favourably with values of about 1.4 for 2 g/m² SR 2508 alone, and 1.3–1.5 for 0.75 g/m² Ro 03-8799 at the same doses, and with 1.3 for 1 g/m² misonidazole. The overall clinical value of the combination will, of course, depend on the total cumulative doses achievable in fractionated regimes.

In summary, we have shown that a single dose of 3 g/m² SR 2508 can be combined with 0.75 g/m² Ro 03-8799, giving a clear potential for therapeutic advantage without increased toxicity. This is now being explored further using a multiple dose schedule.

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(The Editors do not hold themselves responsible for opinions expressed by correspondents)

Field coverage in digital grey-scale fluorography of the chest

THE EDITOR—SIR,

In 1984 Cowen et al introduced a digital radiographic imaging technique which uses a large-field X-ray image intensifier as the primary image detector – digital grey-scale fluorography (DGF). In this preliminary investigation of the DGF technique, images covering a wide variety of anatomy, including the chest, were presented. Further to this, a clinically based survey of the effectiveness of DGF in chest imaging was set up, and the initial findings have been presented by Fowler et al (1985). This study confirmed the diagnostic promise of the DGF technique but highlighted the problem of the limited field coverage provided by the 36 cm X-ray image intensifier. Indeed Fowler et al found it necessary to take two exposures on each patient, one of the upper thorax which included most of the lung fields, and the other which included the lung-bases, mediastinum and the upper abdomen. In conclusion they indicated that if DGF imaging is to prove successful in chest imaging it will be necessary to use an X-ray image tube which provides full coverage in a single exposure.

We have measured the effective field coverage of the 36 cm X-ray image intensifier in DGF using an enlarged version of Leeds Test Object type M1 (Hay et al, 1985). The test object was attached to the input window of the X-ray image intensifier, and the geometrical arrangement used by Fowler et al (1985) was reproduced (*i.e.* an SID of 1 m was used). Under those conditions the effective field coverage in DGF measured approximately 33 cm in diameter. In comparison, conventional radiographic images of the chest traditionally are produced on 35 cm × 35 cm square film or 43 cm (vertical) × 35 cm (horizontal) film. This would indicate that to provide coverage equivalent to these film formats, X-ray image intensifiers of effective input diameter of at least 50 cm and 55 cm, respectively, would be required.

As the question of anatomical coverage has such important consequences for the future development of DGF, we decided to investigate the diameter of X-ray image intensifier required to provide total coverage of the thorax in the majority of patients. To this end a limited survey of the dimensions of patients undergoing chest radiography in Room 2 of the Diagnostic Radiology Department of the General Infirmary was carried out. The chest radiographs were those produced by a Siemens 43 cm (vertical) and 35 cm (horizontal) Thoromat film-changer using a source to image receptor distance of 1.8 m. The chest radiographs were placed on a light box and were compared with a transparent template inscribed with three concentric circles of diameters 40 cm, 45 cm and 50 cm. For each patient the diameter of circle which encompassed the clavicles and both lung bases was noted. A total of 152 patients were surveyed over a period of 3 days during one working week. The size of the sample taken in the survey was dictated by the necessity to minimise disruption of what is the busiest X-ray room in the Department. As far as it is possible to judge from the comments of the radiographic staff, the 152 patients provided a representative sample of the typical workload of the chest X-ray room. No children were included in the survey as they are examined in a separate, paediatric X-ray Department. Patients were categorised in several ways. Firstly they were categorised according to age, viz. adolescents (13 to 18 years), adults and elderly people (over 60 years). The radiographic staff were asked to give a subjective classification with regard to patient morphology including stature (height) and build (chest size). Not all of the patients could be imaged using the Thoromat. Six patients were unable to stand, even for a short time, and therefore had to be radiographed in a supine position using a 35 cm × 43 cm cassette. Three very large patients were radiographed in the erect position using a 35 cm (vertical) × 43 cm (horizontal) cassette.

The findings of the survey are presented in Table I. All the chests radiographed could have been reproduced fully using an X-ray image tube which has an effective input field diameter of 50 cm. Reducing the effective diameter by 5 cm only reduced the number of chests accommodated by one. On the other hand, a reduction in diameter to 40 cm produced a marked reduction in the number of patients accommodated. The survey therefore suggests that an X-ray image tube which can provide an effective field coverage of 45 cm will be able to satisfy the majority of chest examinations and should provide equivalent or even superior performance, in terms of patient coverage and equipment flexibility, to the standard chest changer. Given the advantages of DGF image processing, we suggest that such an X-ray image intensifier could form the basis of a practical digital chest imaging system for the patient population served by the General Infirmary.

TABLE I

CHEST SURVEY RESULTS

Total number of patients surveyed	152
Males	77
Females	75
Nos of patients examined	
Children	0
Adolescents	4
Adults	80
Elderly patients	68
No. of patients of	
Short stature	58
Medium stature	62
Tall stature	32
No of patients of	
Small build	36
Medium build	75
Large build	41
No of patients radiographed on the Thoromat	143
In a supine position	6
In an erect position	3
No of patients whose chest fitted the	
40 cm template	109
45 cm template	151
50 cm template	152

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We wish to thank Miss A. E. Hawkswell, Superintendent Radiographer at the General Infirmary at Leeds, for her assistance in this survey

Yours, etc.,
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Solitary thyroid nodule: what to do?

THE EDITOR—SIR,

In "A prospective study of thyroid ultrasound scan in the clinically solitary thyroid nodule" (Walker et al, 1985) the authors state that solitary thyroid nodules are rarely malignant. However, the 10–20% incidence of malignancy in a nodular thyroid (Rojeski & Gharib, 1985) can by no means be called rare and this is higher in the solitary nodule than in a multinodular goitre. The authors advocate surgery for solid and mixed solid–cystic nodules and conservative treatment for cystic nodules, but a survey of 16 series has shown that 7% of cystic nodules are also malignant (Ashcraft & Van Herle, 1981) Toft (1985) states that cysts are best treated by aspiration, but surgery is indicated for cysts larger than 4 cm, if the cyst fails to reduce in size or disappear within 3 months, or if reaccumulation occurs after aspiration Aspiration should be used routinely in the management of cystic nodules as a diagnostic and therapeutic intervention (Rojeski & Gharib, 1985) as it may identify the cyst as benign or malignant and may cure the nodule (Clark et al, 1979).

The only question in a solitary thyroid nodule is: is it benign or malignant? The authors correctly conclude that ultrasound does not provide the answer. It should not be done routinely in evaluation of a thyroid nodule (Rojeski & Gharib, 1985). In this context, fine-needle aspiration biopsy (FNAB) is the most sensitive and specific test (Van Herle, 1982) and is the best initial diagnostic step.

Yours, etc.,
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Scapular fracture

THE EDITOR—SIR,

I read the comments on our paper (Banerjee & Field, 1985) on the scapular fracture following a water-skiing accident with great interest (Rao, 1985). I accept the importance of considering developmental defects in the ossification of the scapula in the differential diagnosis of scapular fractures (Cigtay & Mascatello, 1979). In the case we described, however, this would seem to be a most unlikely cause of the abnormal radiograph on three counts

Firstly, our case was associated with trauma whereas the cases previously described were not. On examination, there was a large haematoma over the body of the left scapula corresponding with the fracture site in which a central portion of the scapula was avulsed from the peripheral part. Secondly, the fact that the site of the avulsion fracture corresponded to the site of origin of the infraspinatus muscle must surely be more than just coincidence. This is the muscle which would have been suddenly stretched while the young man fell backwards trying to stabilise himself while losing control during the water-ski race. Thirdly, the fracture we described was a ring or avulsion fracture. In developmental ossification defects of the scapula, the lucencies are usually multiple and sharply demarcated with sclerotic borders (Cigtay & Mascatello, 1979).

. I do agree, however, that in the absence of trauma, the diagnosis of developmental osseous defects of the scapula, although very rare (McClure & Raney, 1975), should nevertheless be borne in mind.

Yours, etc.,
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Book review

X-ray Imaging Equipment—An Introduction. By Euclid Seeram, pp. xxii + 543 + index + refs, 1985 (Charles C. Thomas, Illinois), $44.50.

ISBN 0–398–05078–3

This book is intended to be an up-to-date text dealing with equipment employed in X-ray medical imaging and aimed at radiographers and radiologists in training. The book is 588 pages long and is divided into three parts: A, B and C.

Part A is divided into two sections, A and B, with Section A itself divided into 10 chapters and two parts. Part B, comprising four chapters, is divided into Sections C and D whilst Part C is Section E. Having unravelled the structure of the book it is then possible to consider the content. Part A, Section A covers X-ray tubes and generators, including timers, tables and tube supports, tomographic equipment, portable/dental units and other techniques including mammography, high-kV techniques and photofluorography. Part A, Section B deals with image intensifier/TV systems. Part B, Sections C and D covers digital image processing and computers and their application in CT and digital radiography. Finally, Part C, Section E deals with quality assurance.

Overall, I found it impossible to form a positive opinion of this book. Although it is beautifully presented and obviously contains some worthwhile and readable material, it falls short of expected up-to-date requirements in both content and composition.

According to the dust cover, "This text gives its readers a firm footing on the basic theoretical aspects of X-ray imaging equipment . . .". Only approximately a dozen or so, extremely simple, mathematical expressions are included in over 500 pages, indicating that this aim is hardly justified. This is further indicated by the fact that, for instance, image reconstruction in computed tomography is covered in two sentences. The dust cover also indicates that NMR imaging is included but, apparently it is included only on the dust cover.

The major omission from the book concerns screen/film combinations. These constitute the most widely used type of equipment in X-ray imaging. Their omission contrasts with the inclusion of electrostatic imaging techniques as well as some experimental digital radiographic methods.

There are several more "local" anomalies/omissions occurring in the text, some examples being the following.

Chapter 2, Part I: "Radiation dose is inversely proportional to the square of the distance (inverse square law). This means that the greater the distance between the source of radiation and the exposed person, the smaller the radiation dose". This statement, which is applied to patients, seems ideal for a confusing multiple choice question.

Chapter 5 covers X-ray tubes and includes reference to the use of compound materials in the anode. These are not discussed in relation to their role in matching both thermal conductivity and expansion properties of compound anode disks.

Chapter 19 is concerned with quality assurance concepts. Although the book deals with X-ray equipment and is aimed at radiographers in training, this chapter occupies only some 16 pages and gives very little information on either test equipment available or its use

When attempting to formulate an opinion on someone else's published material, especially when it has involved so much obvious sweat and toil, the old adage "if you can't say something nice . . ." comes to mind. I do have the distinct impression that a worthwhile and readable text is attempting to manifest itself but I feel that more work is required by the author in order to achieve this aim. The book also highlights the great difficulty encountered in trying to produce a text which deals with X-ray imaging equipment in anything but superficial descriptive terms, when it is treated in isolation from some of the more fundamental scientific imaging principles which underpin many of its design requirements.

B. M. MOORES

BIR Bulletin

April 1986

90 Years of X rays: a celebration

This one-day celebration organised by the British Association for the Advancement of Science in collaboration with the British Institute of Radiology and the National Radiation Protection Board was held at the Royal Society, London, on November 8, 1985.

The purposes of the meeting were: to honour W. C. Röntgen for his discovery of X rays, to survey the benefits arising from their use, to review the body of adverse effects, and to describe the principles and practice of radiological protection.

The international audience of over 150 people represented a broad cross-section of society and included specialists from medicine, science and industry; employers and trade union officials; politicians; members of pressure groups; and the media.

Sir George Porter, F.R.S., President of the BA, welcomed the audience and speakers and gave a brief history of the Royal Society, which he said was honoured to provide the venue for such an important occasion.

After a short introduction by the chairman, Sir Frederick (now Lord) Dainton, F.R.S., Chairman of NRPB, Professor D. Harder, Institute of Medical Physics, University of Göttingen, gave a talk entitled "Röntgen's discovery: how and why it happened". He described the events leading up to Röntgen's famous discovery of "a new kind of rays" and the immense practical and scientific consequences, from the sudden birth of X-ray diagnosis and radiotherapy to the formulation of the theory of relativity and atomic physics. Professor Harder attributed Röntgen's discovery to "his extraordinary experimental abilities, his great experience and reading, and the deep consciousness of all his doing".

There was a short break in the scientific programme while a presentation was made by the College of Radiographers and the International Society of Radiographic and Radiological Technicians to Mr E. Streller, who retired as Curator of the Deutsches Röntgen Museum, Remscheid, West Germany, in August 1985.

The next speaker, Professor F. W. Spiers, formerly Professor of Medical Physics, University of Leeds and now a consultant to NRPB, gave a talk entitled "Early protection and radiological physics" in which he described the problems that beset the use of X rays and how these were resolved in the modern practice of radiation dosimetry and protection.

Professor I. Isherwood, Professor of Diagnostic Radiology, University of Manchester, and immediate Past President of the BIR, described the development of diagnostic radiology from the early use of X rays to show the position of bones and bullets to the current detailed three-dimensional imaging abilities of computed tomography and magnetic resonance imaging. He stressed that three-quarters of the world's population are unlikely ever to be radiographed and that 80% of all X-ray examinations are essentially simple procedures. He suggested that digital X-ray radiology, by providing the facility for long-range image transmission and computer stores of basic information, together with continuing advances in intelligent knowledge-based systems, could indicate a longer term approach to the moral dilemma of high technology in some parts of the world and deprivation in others.

Professor R. J. Berry, Professor of Oncology, Middlesex Hospital Medical School, Vice-President of the BIR, discussed the therapeutic use of X rays from the low-energy X rays produced by the early machines to the megavoltage electron linear accelerators which are now the mainstay of the modern radiation oncology department. While acknowledging the future role of particle radiations for the treatment of cancer, he stressed that 90 years after Röntgen's discovery of the X ray, the modern successor to his machine remains the most important modality after surgery in the treatment of cancer.

The final speaker, Dr D. Beninson, Chairman of the International Commission on Radiological Protection, discussed the biological basis for radiation protection standards and their implications for policy. He defined the objectives of radiation protection of individuals as the prevention of the occurrence of non-stochastic effects and the limitation of the probability of stochastic effects to levels deemed to be acceptable.

Along with an exhibition of historic items from the Science Museum, the diversity of the visual presentations which accompanied each talk added a fascinating dimension to this survey of imaging. Perhaps the greatest contrast demonstrating the 90-year span of development was provided by the tentative ghostly tones of Röntgen's radiograph of his wife's hand and the dazzling lucidity of the "rotating" skull captured on video by computed tomography.

A question and answer session concluded this instructive and enjoyable 90th anniversary celebration in the beautiful rooms of the Royal Society overlooking St James' Park.

The abstracts of papers presented at this meeting will be published in the *British Journal of Radiology* later this year and it is hoped to assemble a reference set of papers with accompanying slides for the historical collection of the BIR.

J. B. McGuigan

BIR Welsh Branch: 1985 Autumn Meeting

The Autumn Meeting of the Welsh Branch of the British Institute of Radiology was held at the University Hospital of Wales, Cardiff, on November 23, 1985 under the chairmanship of Dr Rosemary Anderson. The scientific programme included the papers from colleagues in departments of radiology in Cardiff with abstracts given below.

The Summer Meeting of the Welsh Branch of the British Institute of Radiology will be held at Prince Charles Hospital, Merthyr, Mid Glamorgan, June 13–14, 1986 Dr John Parker, Consultant Radiologist, will be acting as convenor

Congenital lung disease

Margaret R. Jones

Developmental anomalies of the respiratory tree may be subdivided into those associated with the vascular supply and those resulting from abnormal development of the primary lung bud. This paper was confined to the latter category.

A series of cases presenting in the last 10 years to Llandough Hospital was considered. The series comprised patients suffering from bronchial atresia, congenital cystic bronchiectasis, congenital cystic adenomatoid formation and congenital lung cysts Several cases of sequestrated segment were included along with one rare example of oesophago-bronchial fistula to the left lower lobe in an adult It was emphasised that these lesions frequently present in adults and the possibility of a congenital aetiology should be considered.

Hydatid disease in South Wales

Richard Clements, M.A, F.R.C.S., F.R C.R

University Hospital of Wales

The overall incidence of hydatid disease in Wales is currently 0 4 cases per 100 000 patients per year. The highest incidence is in South Powys with 3 8 cases per 100 000 patients per year. Forty-eight patients with histologically proven hydatid cysts underwent radiological investigation in Cardiff between 1975 and 1984: most of these patients acquired the disease in the UK. The hydatid cysts were located in the lungs, pleura, liver, kidneys, and brain. Hydatid cysts of the right adrenal gland, the lumbar spine, the greater omentum, the ischiorectal fossa and the broad ligament were also investigated The radiological features of some of these cases were presented Fine-needle aspiration of a hydatid cyst was unwittingly performed in two patients, and two further patients underwent percutaneous transhepatic cholangiography during the investigation of obstructive jaundice None of these four patients developed an anaphylactic reaction The risk of anaphylaxis with fine-needle puncture of a hydatid cyst may be lower than is generally accepted

Computed tomography in thoracic vascular disease

David A. Robinson

Computed tomography has a small but growing place in the imaging of thoracic vascular abnormalities Its role was illustrated in the context of SVC obstruction, proximal and peripheral pulmonary vascular abnormalities and aneurysm of the aorta. The status of coronary vein grafts can also be assessed in a sensitive and specific way with dynamic axial tomography. Cases were presented where CT appeared to be more sensitive than conventional aortography in the diagnosis of thoracic aortic dissection. The future role of MRI in vascular work was mentioned briefly.

Radiology of ischaemic heart disease

M Hayward

Not all cases of ischaemic heart disease are due to atheroma, and non-atheromatous causes were briefly reviewed Several techniques related to IHD were discussed, including the role of chest radiography Angioplasty was briefly considered and several examples were shown. A general review of nuclear cardiology was presented firstly, infarct avid imaging with technetium-labelled pyrophosphate and secondly, myocardial perfusion using thallium. The advantage of using tomography was stressed The principle of gated studies using red-cell labelling was reviewed and the various modes of presentation, *i.e.* cine mode, phase, and amplitude studies, described. Their ability to show regional wall motion abnormalities both at rest and at stress, and for the assessment of ventricular aneurysms was demonstrated Finally, speculation as to the future role of MRI in cardiac disease was discussed

Trauma: some new solutions to old problems

L A Williams

Difficulty in diagnosing impacted femoral neck fractures was pointed out A survey at Cardiff Royal Infirmary of 690 cases found 40 patients with normal initial radiographs Radionuclide bone scans were performed on this group Thirteen fractures were found, 11 subcapital, two intertrochanteric In two patients no action was taken and displaced fractures occurred. There was one false negative scan, but on review this examination was technically inadequate.

Osteoarthritis does not detract from the value of the scan. Patients with osteoarthritis do not sustain subcapital fractures due to thickness of femoral neck; these patients all had intertrochanteric fractures. A few horizontal subtrochanteric fractures were found. These were all pathological

Investigation of choice is CT for suspected acetabular fractures, as it enables demonstration of intra-articular fragments which may prevent closed reduction Posterior dislocations of hip may be missed on an AP radiograph unless internal rotation with absence of lesser trochanter is appreciated If there is any doubt, CT clearly demonstrates the abnormality. Scaphoid fractures can always be diagnosed on initial radiographs, provided there is a good oblique view with ulnar deviation. Ten day follow-up recommendation is probably a myth. Bone scans can again be helpful in excluding fractures and in demonstrating other missed carpal fractures.

BIR Awards 1986

1986 Barclay Medal
The Barclay Medal is awarded to Dr D. K. Bewley for his contributions to the Journal over many years on the physical and biological aspects of neutron therapy and on other topics in radiation physics.

1986 Barclay Prize
The Barclay Prize is awarded to Professor M. N. Maisey and his team at Guy's Hospital, London, for their contributions to the Journal on radionuclide procedures for diagnosis and clinical investigation in cardiology and other fields.

1986 Röntgen Prize
The Rontgen Prize is awarded to Professor N. M. Bleehen and his team at the Clinical Oncology and Radiotherapeutics Unit, Cambridge, for their contributions to the Journal on hyperthermia and radiosensitisers.

The awards will be presented at the Conversazione on June 19, 1986, to be held at the rebuilt Royal Society of Medicine.

Obituary

G. B. Schofield, M.B., Ch.B. F.F.O.M., A.I. Mech. E.

The sudden death last summer of Geoff Schofield at 60 years of age deprived occupational medicine of one of its most respected practitioners. Radiology has also lost, as he used the medical skills he had acquired while working for a long time in radiological protection in close co-operation with radiological colleagues, particularly in Cumbria. He was the Mackenzie Davidson Memorial Lecturer in 1979 and his paper, "Biological control in a plutonium production facility", on that occasion was published in the *British Journal of Radiology* in May of the following year. This was a field of work in which he had made himself a national and international reputation. He had worked at the Windscale (now Sellafield) Works for about 27 years and had acquired a unique experience of all the medical aspects of radiological protection, with particular reference to the chemical parts of that problem, but he had also written and lectured widely on epidemiology of the health of radiation workers and of the appropriate preparations to make for emergency procedures.

He had an unusual background, in that before entering medicine he had served in the Royal Navy in engineering and perhaps it was this which gave him his great capacity to work well with other scientists and engineers, that type of co-operation lies, of course, at the heart of successful performance in the field of radiological protection. It was probably his capacity to work with people, to get their interest and their friendship that made his career so successful. He was a delightful companion with wide interests and an ability to relate well to all sorts and conditions of men. The field in which he worked can be a contentious one but he provided a very fine example of someone whose integrity, honesty and friendliness was reassuring to all those, be they workers or others, who had to form a view on the relative safety in which they were employed or lived.

Friends and colleagues all over the country and abroad will miss him badly but the loss obviously falls hardest on his wife Joyce and his two sons now well launched into the medical profession. His life was based on a happy domestic foundation and the family have been much in the thoughts of all those who know them.

Kenneth P. Duncan

Radiology in Japan

Radiologists in Japan and Britain are not easily comparable since the origins of their modern medical practices are very different and the specialties within medicine have evolved differently. Radiology in Japan ranks as only a minor specialty, as against the much more numerous and powerful specialties of surgery and internal medicine, and radiology itself is defined loosely in Japan, there are no formal or legal definitions to the term, nor are any national qualifications (apart from the national physician's licence) needed to practise as a radiologist. The specialty is comparatively small, loosely organised, and overshadowed by larger groups. Most radiologists tend to work in large hospitals where the expensive, sophisticated equipment tends to be concentrated, but as there are proportionately fewer large hospitals in Japan than there are in Britain, the number of places where they can work tends to be restricted.

Radiologists are not satisfied with this situation. The former Dean of Tohoku University Medical School, himself a radiologist, complained that the situation, in that region of Japan especially, was so bad that its Department of Radiology, in one of the leading medical schools in Japan, had had difficulty in filling its complement of places, that it was deterring potential applicants from joining and that the scarcity of radiologists was leading into a vicious circle, since work needing to be done by specialists was either being done by others or not being done at all. However, as I hope to show, the situation in Japan has lately begun to turn in favour of specialist radiologists, so the outlook is not too pessimistic in the long run.

There are a number of explanations for the lack of specialist development, doctors from the very beginning simply elected their own chosen field and practised and conducted research in their own clinics. There were in fact no hospitals in the pre-industrial era, nor even any kind of public welfare system. However, physicians (practising Chinese medicine) with a strong emphasis on dispensing medicine were numerous. The modern hospital in Japan is a comparatively recent foundation, having had its beginnings in a kind of living quarters for outpatients needing to be near their physician for treatment. The patient went to the doctor who was, from the start, a practitioner equipped with his own place to carry out his profession.

Although the modern hospital is by now very well established in Japan, it still bears some unusual characteristics: many large hospitals, which are mostly private institutions, have developed to their present size during the life-time of their founders; 70% of hospitals in Japan are in private hands and as they have to make a profit to survive, there is little employment for "unnecessary" specialists. A further feature of Japanese hospitals is that patients tend to go direct to the outpatient department of a hospital when seeking treatment, rather than through a general practitioner. In fact there are no general practitioners, nor indeed any specialists in the British sense.

Another feature of health care in Japan is that it is physician-centred, physicians occupy the central position and, surrounded by their helpers, they minister to patients on the periphery of the circle, whereas in Western medicine the patient is generally seen as being in the centre of the circle with the various helpers working on him from the periphery. I was told more than once that the physician in Japan was "almighty", and they certainly are powerful, by the terms of their licence they are empowered to operate all varieties of medical equipment, whatever the specialty.

All this has a bearing on the development of radiology in Japan. The emphasis is on the physician, rather than his specialty, and the most powerful specialties are those of the largest groups, *i.e.* surgeons and internal medicine specialists. Some comparative statistics about radiologists may show some differences. In England in 1981 there were 1588 radiologists (whole-time equivalents), which represented 5% of the total of 32141 specialists, in Japan in 1982 there were 1788 out of a very much larger total number of physicians (160379), or just over 1%, who declared their leading specialty to be radiology, and about 7% who gave radiology as one of their specialties. The proportions in Japan are therefore smaller and they are, in any case, rather differently calculated, being based on those who describe themselves as radiologists, rather than on membership of the association, which is not made up exclusively of radiologists. Again, as has been mentioned, there are proportionately fewer large hospitals in Japan, in 1982 in England and Wales there were 33% of hospitals with 500 or more allocated beds whereas the figure in Japan for the same year was 20% In other words, smaller hospitals still predominate in Japan, and it is these which are not so likely to be able to offer employment to the specialist working exclusively in radiology.

What about the training of physicians and how do they come to choose their specialties? In Japan, training of the various specialists is not carried out by the professional associations but within the faculties of medicine in hospital medical schools. The Japanese have always favoured "vertical" relationships epitomised in the family or the place of work rather than in "horizontal" associations typically seen among professional colleagues. In medicine in Japan the faculties of medicine play a powerful role and they control the shape of the profession and the balance of specialties. Professors, as heads of departments, install their nominees in hospitals falling within their influence (that is to say, founded or originally staffed by them). As an example, a medical school having helped to set up a hospital will thenceforth expect to place its own graduates in vacancies occurring there. For instance Tokyo University's medical school was responsible for originally setting up the medical school of Tohoku University and although this university has for long been independent of Tokyo University (and has established its own tributary medical schools elsewhere) the structure of the medical school still reflects Tokyo's preference for the two older-established clinical specialties of surgery and internal medicine. Radiology, a relatively late arrival as a technological specialty, still does not possess equal status and this is important in the Japanese context because the physician's primary loyalty is not to his hospital or to his professional specialty but to the university department from which he graduated. In contrast to America and Europe, the horizontal relationships linking colleagues working in the same fields but in different localities are weak

The picture at Tohoku University illustrates the conservative tradition, particularly strong in the region north of Tokyo. Until 1964 clinical radiology was decentralised and radiographic services were available as a service to the hospital. Since then there has been a steady trend towards centralisation, but progress has been slow because of opposition from the other specialties and it is only since April 1985 that all the services have come under the control of a radiologist. But the university hospital is still far from having a central imaging department, as is the trend elsewhere in Japan, and there are serious shortages of staff to do radiodiagnostic work, about half of which is carried out by other specialists. Clinical nuclear medicine and radiotherapy is of course entirely operated by specialist radiologists The result of having so few coming forward to become radiologists in this particular hospital is that members of the department are heavily overworked and as we have seen, these conditions appear to deter others from joining. But the situation will improve owing to the current oversupply of graduates from medical schools who will no longer be as free as they were to go into the most popular specialties and radiology is likely to benefit from this situation

In truth, the situation in Japan does not encourage specialism The clinician who is a member of large groups like surgery and internal medicine has, at present, all the benefits available to the specialist radiologist He is automatically entitled to membership of the Japan Association of Radiologists To take an example of a surgeon needing to use radiography, he will probably do without a specialist's interpretation, because even if he wanted to consult a specialist, that person would be too busy So he goes ahead on his own In Europe or America a second opinion would be more easily available and would of course be a necessary protection in a case brought against him for professional malpractice In Japan, with litigation at a very low level, these dangers are not so evident, but they will probably grow and, moreover, there is a general trend whereby patients are coming increasingly to expect diagnosis by specialists.

What is the professional association doing about this situation? As has been explained before, it is mainly an academic association where members meet to discuss papers, and it has little political power. It is an active learned society of about 3000 members Any physician is eligible for membership and others with an interest in radiology are, with suitable references, accepted. There are about 40 members at Tohoku University but a minority are members of the Department of Radiology

Radiologists have recently called for a fundamental shake-up of the system, exhorting radiologists to make powerful efforts to assert their own separate identity and to convince others that it is in their own interest to make more use of specialist radiologists. They say that Japan has fallen 10 years behind America and that there must be specialist training carried out under the auspices of the professional association, and that a syllabus of fundamental radiology, which must include nuclear medicine, will have to be developed.

One solution might be to define more closely the area of work of the various specialties, thus legally protecting the territory of the radiologist, but it seems unlikely that this will come about. There does, however, seem to be a need for the various specialist associations to define their responsibilities more clearly and to increase the training in and provide qualifications for skills at present unrecognised, *e.g.* in radiodiagnosis. The role of the medical physicist is another grey area, not yet being formally recognised There does seem to be no reason why these functions should not develop, although it is interesting that their shape is likely to be dictated by emerging technology, so the situation is flexibly poised to meet future developments.

The implications of the effect of new technology may be seen in figures for 1984(*) and 1985 for Japan, given below

	No. of units
X-ray CT	3294
NMR CT	40
Positron emission CT*	9
Single photon emission CT*	137
Digital angiography*	45
Ultrasound*	15 522

Taking X-ray CT units as an example, these, each costing between £35 000 and £55 000 per unit, have grown enormously in number. Between 1976 and 1981 the count for the whole of Japan increased from 454 in 1978 to 1693 in 1981, a factor of 3.7 times. In 1984 there were 2821 such units and as can be seen there has been a further expansion since then of 18%. In regional terms, for the whole of the north eastern region of Japan, with a population of about 10 million, there are 194 hospitals with at least one of these units, and there are 231 X-ray CT units in all in this region.

A full examination of the meaning of such generous provision of sophisticated medical equipment (and the list given above is by no means complete) is of course impossible here, but as the technology becomes even more abundant and easier to operate, there is going to be an effect on the appropriate professional specialties, including radiology which occupies a very modest position at present that is probably not indicative of its true worth. The as yet structurally undeveloped professional associations in Japan seem to be the best placed to take up the challenge

I H F. Kerr

BIR Calendar Events

Unless otherwise indicated, enquiries about the following events should be addressed to the Assistant Secretary. Programme, British Institute of Radiology, 36 Portland Place, London W1N 3DG (Tel. 01-580 4085)

The meetings are at 36 Portland Place unless otherwise stated

Attendance is open to non-members

Annual Dinner
April 10, 1986
Holiday Inn, Bristol

Annual General Meeting of the BIR
May 14, 1986
Members only

Safety of Diagnostic Ultrasound and Presidential Address
May 15, 1986 at 2 pm.
Middlesex Hospital Medical School, London W1
Includes the Presidential Address at 5.30 (open to non-registrants) to be given by Dr P N T Wells. "The prudent use of diagnostic ultrasound"
Joint BIR/BMUS/RSM/COR/IPSM/-RCOG/RCR meeting

Radiology '86
April 9–11, 1986
Bristol
44th Annual Congress and Exhibition

Incorporating the joint spring meeting of the Institute with the Royal College of Radiologists and the Section of Radiology of the Royal Society of Medicine. It will be held in the picturesque setting of the Bristol waterfront

The scientific programme (CME accredited) will encourage discussion of contemporary aspects of the radiological sciences and will include

BIR Mackenzie Davidson Memorial Lecture (Dr A. Margulis. "Advances in Technology and Their Impact on Medicine")
BIR Mayneord Lecture, sponsored by 3M UK Plc (Mr G Higson: "Seeing Things More Clearly")
RCR George Simon Lecture (Professor N. M. Bleehen "Raleigh's Revenge")
All-day Seminar—Buying for Radiology organised with the Association of National Health Service Supplies Officers
All-day Seminar—Biological Basis of Radiological Protection and its Application to Risk Assessment
Proffered Papers
Large Technical and Scientific Exhibition
Annual Dinner, April 10

Progress in Tumour Radiobiology
May 16, 1986 at 11.00 am
Organised by the Radiobiology Committee (proffered papers).

The Assurance of Quality in Medical Imaging
May 21, 1986
Middlesex Hospital Medical School, London
All-day meeting organised by the BIR Quality Assurance Working Party in conjunction with Industry Committee. Speakers include radiologists, radiographers, physicists and engineers from the NHS and industry

Conversazione
June 19, 1986 at 7 00 pm
Royal Society of Medicine, London W1
Incorporating the Silvanus Thompson Memorial Lecture "Seeing through Illusion", by Professor R. L Gregory.

Joint RCR/BIR/RSM Autumn Provincial Meeting; RCR Annual General Meeting
September 11–13, 1986
University of Sheffield
Organised by the RCR. Further details from the Meetings Secretary, The Royal College of Radiologists, 38 Portland Place, London W1N 3PG (Tel. 01-636 4432/3).

Annual General Meeting
The AGM of the British Institute of Radiology will be held at 4.30 pm on Wednesday, May 14, 1986 at 36 Portland Place, London W1.

Press Releases

Imtran in medical work

Worldwide interest is now being shown in a new portable British device which allows high quality black and white medical pictures to be sent along ordinary telephone lines This latest piece of technology from British Telecom is called Imtran (short for image transmission) and consists of an all-in-one microprocessor controlled transceiver It weighs less than 11 pounds and fits neatly into an average-size attache case

Imtran uses slow-scan television techniques to transmit detailed black and white images through the public telephone network to a small monitor screen

Its versatility was demonstrated in the autumn of 1985 when live body-scan pictures were sent from Bristol's Frenchay Hospital to Brisbane for the 36th Annual Congress of the Royal Australian College of Radiologists. Anyone wanting further information about Imtran should contact British Telecom's Imtran Marketing Manager John Ling on Bristol (0272) 295769 or on Freephone Imtran. His address is Mercury House, Bond Street, Bristol BS1 3TD

New world standard covers radiation field from rotating anode X-ray tubes

Designers and manufacturers of electrical medical equipment will welcome BS 6628: *Determination of the Maximum Symmetrical Radiation Field from a Rotating Anode X-ray Tube for Medical Diagnosis*. It is identical to IEC 806-1984. BS 6628 is applicable to X-ray source assemblies and X-ray tube assemblies containing rotating anode X-ray tubes for use in medical diagnostic radiology for techniques in which the X-ray pattern is received simultaneously in all points of the image reception area.

Unless otherwise specified, the standard is applicable to an X-ray tube assembly with a brand-new rotating anode X-ray tube It describes a method for the determination of the greatest geometrically symmetrical radiation field at a specified distance from the focal spot for which the percentage air kerma rate along the major axes does not fall below a permitted value.

Copies of BS 6628 may be obtained from the Sales Department, British Standards Institution, Linford Wood, Milton Keynes MK14 6LE. Price £16 50 (£6 60 to BSI subscribing members).

Video tapes on coronary artery disease

On September 9 and 10, in Washington, DC, the American College of Nuclear Physicians and the Society for Nuclear Medicine cosponsored an international symposium on the Role of Noninvasive Imaging Modalities in Clinical Decision Making. Coronary Artery Disease. A video tape featuring all the speakers and slides presented during that meeting is now available.

Cardiologists, radiologists, nuclear physicians, regulators, and third party payers gathered at the Symposium for a candid dialogue that examined cost containment and reimbursement as it affects clinical decision making in the detection of coronary artery disease Many of the newest technologies for diagnosing or managing today's coronary artery patient were examined, including thallium myocardial tomography, ultrasound, nuclear magnetic resonance, and positron emission tomography—all unknown five years ago

At the same time, symposium attendees and presenters grappled with the reality that despite the advent of many promising new techniques, cost-containment efforts have resulted in fewer imaging procedures and a premium being placed on services defining protocols that result in shorter hospital stays and increased use of outpatient facilities In the words of one attendee, the Symposium presented "a blend of clinical data and contemporary economic reality."

The two-cassette video tape is available for $125 in Beta or VHS format For more information, or to place an order, contact CNTV, Suite 700, 1101 Connecticut Avenue, NW, Washington, DC 20036 (Tel. 202-429 5100)

DSL300 Sector linear scanner

The new DSL300 combined sector linear real-time scanner from Diagnostic Sonar Ltd, is extremely compact considering the image quality produced together with a range of facilities usually found only in larger, more expensive equipment. The DSL300 is the most advanced and user-friendly system Diagnostic Sonar has offered

The newly developed analog switch and 64 greylevel digital scan converter, with image processing such as line-to-line and frame-to-frame correlation, give superior image quality and a video output. The latter can be used to record directly on to video tape recorders, multiformat cameras and image printers for keeping permanent records The new multifeature scanner trolley includes a couplant warmer, miniature test object, linear and sector transducer holders and a convenient accessory tray.

For a brochure, please request Publication No 124 from Diagnostic Sonar at the following address: Baird Road, Kirkton Campus, Livingston EH54 7BX

Library news

The BIR Library is open weekdays 9am–5pm

The Librarian, Mrs Gunnel Ingham, is in attendance Tuesdays and Thursdays 11am–4pm; Mrs Diana Jasper, daily 10am–5pm

The journal stock includes more than 100 titles Though journals may not be taken out of the library, there is a photocopy service, also available by post.

Most books (excepting the historical collection) are available on loan.

Further information: telephone 01-580 4085

Recent additions to the Library

Arndt, R D., Horns, J W & Gold, R. H.. Clinical arthrography. 2nd edit 1985

Bleehen, N. M. (Ed.) Tumours of the brain 1986

Dosch, J.-C. Trauma. Conventional radiological study in spine injury 1985

Gifford, D.. A handbook of physics for radiologists and radiographers. 1984

Quimby, E H, Feitelberg, S & Gross, W Radioactive nuclides in medicine and biology 3rd edit. 1970

Rayudu, G. V. S (Ed) Radiotracers for medical application. Vols 1 and 2 1983

Siddiqui, A R. Nuclear imaging in pediatrics 1985

Sprawls, P.. The physics and instrumentation of nuclear medicine. 1981

Wynne-Davis, R, Hall, C. M. & Apley, A. G.. Atlas of skeletal dysplasias 1985

Meetings, Courses, Notices

As a service to our readers, the title, date and place of meetings and contact address will be inserted free of charge: any additional information will be charged at £1.75 per printed line, per insertion. Please contact the Managing Editor.

6th Annual San Diego Resident's Radiology Review Course
April 27–May 2, 1986
San Diego, California
Further details: R. Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113, USA (Tel. 404-641 9773).

Course on Cancer Epidemiology
April 28–May 9, 1986
Holzhau, East Germany
Further details: The Research Training and Liaison Unit, International Agency for Research on Cancer, 150, cours Albert Thomas, 69372 Lyon Cedex 08, France.

1st International Conference on the Clinical Application of Photosensitization for Diagnosis and Treatment
April 30–May 2, 1986
Tokyo
Topics will include tumour localisation and treatment in cancer of various organs, including combined treatment with other modalities.
Further details: Dr Yoshihiro Hayata, Tokyo Medical College Hospital, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan.

International Continuing Medical Education Series
Controversies in Medicine
April 30–May 15, 1986
Paris/Versailles, France

August 14–29, 1986
London, England

Update on Laser Therapy
June 25–July 10, 1986
Heidelberg, Germany

Further details: Dr Barry M. Manuel, Department of CME, Boston University School of Medicine, 80 E. Concord Street, Boston, MA 02118, USA (Tel. 617-638 4605).

Sixth International Symposium: Radionuclides and Nephro-Urology
May 5–7, 1986
Hotel Beau Rivage, Lausanne, Switzerland
Further details: A. Bischof-Delaloye, Division Autonome de Médecine Nucléaire, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne, Switzerland, (Tel: (021) 41 42 48)

Continuing Medical Education Courses

Diagnosis of Lung Diseases in Adults and Children: An Imaging Approach

May 12–16, 1986
Paris, France

Radiology for the Clinician "Lung Diseases: Clinical Problems and Imaging Solutions"

July 7–11, 1986
Venice, Italy

Imaging and Interventional Radiology

September 12–29, 1986
Peking, Shanghai, Hong Kong and Bangkok

Medical Imaging in the Diagnosis of Chronic and Acute Lung Disease

September 22–26, 1986
Edinburgh

Frontiers in GU and Bone Imaging

November 3–7, 1986
Marbella, Spain
Further details: R. Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113, USA (Tel. 404-641 9773).

IV Symposium on the Medical Applications of Cyclotrons
May 28–31, 1986
Turku, Finland
Further details: Scientific Secretary, Robert Paul, Turku Medical Cyclotron Project, University Hospital, SF-20520, Turku, Finland (Tel: (21) 611 611).

Radiology of the Small Intestine
May 31, 1986
John Radcliffe Hospital, Oxford
Fee: £30.00
Particular emphasis will be placed on the small bowel enema technique.
Further details: Dr D. J. Nolan, Department of Radiology, John Radcliffe Hospital, Oxford OX3 9DU (Tel. 0865-817238).

European Gamma-11 Users Meeting
June 4–6, 1986
Guy's Hospital, London
Further details: E. D. Williams, Medical Physics Department, Sunderland District General Hospital, Sunderland SR4 7TP.

Cardiovascular Radiology and Musculoskeletal Radiology
June 12–15, 1986
Salzburg, Austria
Further details: Dr K. H. Barth, Department of Radiology, Georgetown University Hospital, Washington, DC 20007, USA (Tel. 202-625 2891).

Cambridge Meeting on Chest Disease
July 3–5, 1986
King's College, Cambridge
Further details: Dr C. D. R. Flower, Department of Radiology, Addenbrooke's Hospital, Hills Road, Cambridge.

The Leeds Gastroenterology Course for Radiologists
July 7–11, 1986
St James's University Hospital, Leeds
Further details: Mr Frank Moran, Senior Administrative Assistant, Postgraduate Dean's Office, Leeds General Infirmary, Leeds LS1 3EX (Tel. 0532-432 799, ext. 3631).

Nato Advanced Study Institute on: Physics and Technology of Hyperthermia
July 26–August 9, 1986
Urbino, Italy
Further details: Dr S. B. Field, MRC Cyclotron Unit, Hammersmith Hospital, Ducane Road, London W12 0HS.

Computers for the Practising Physician: Update 1986
July 27–30, 1986, New Seabury, Cape Cod, Massachusetts
Further Details: Department of CME, Boston University School of Medicine, 80 East Concord Street, Boston, MA 02118, USA.

Radiation Oncology Physics 1986
July 27–August 1, 1986
Miami University, Oxford, Ohio
Further details: Dr P. A Feller, Oncology Center, The Jewish Hospital, Cincinnati, Ohio 45229, USA (Tel. 513-569 2285)

4th International Congress on Interventional Ultrasound.
August 19–22, 1986
Copenhagen, Denmark
Further details: Spadille Congress Service, DK-3100 Hornbaek, Denmark

Physics and Biology of Radiology
September 1–5, 1986
San Diego, California
Further details: R Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113, USA (Tel 404-641 9773)

International Symposium on Radiotherapy in Developing Countries: present status and future trends
September 1–5, 1986
Vienna
To be convened by the International Atomic Energy Agency. Papers to be submitted by February 14, 1986.
Further details: M Pankhurst, Atomic Energy Division, Department of Energy, Thames House South, Millbank, London SW1P 4QJ (Tel. 01-211 6850).

8th International Radiology Congress: Radiology in Salzburg
September 7–13, 1986
Salzburg, Austria
Further details: Dr D. Beatty Crawford, Department of Radiology, University of Connecticut Health Center, Farmington, CT 06032 USA (Tel. 203-674 3322).

Paediatric Radiology Course
September 8–10, 1986
Sheffield
Basic paediatric imaging for consultants and senior registrars to enable them to face problems in the DGH and FRCR.
Further details. Dr G. M. Steiner, X-ray Department, Sheffield Childrens Hospital, Western Bank, Sheffield S10 2TH (Tel. 0742-71111).

4th Midlands Course in Otoradiology
September 12–13, 1986
Coventry
Further details Miss M. Adams Centre Administrator, Warwickshire Postgraduate Medical Centre, Stoney Stanton Road, Coventry CV1 4FG.

Sonographers' Update and Review
September 12–14, 1986
San Diego, California
Further details: R. Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113, USA (Tel. 404-641 9773).

4th International Selectron Users Meeting
September 14–17, 1986
British Columbia, Canada
Further details. Dr S M. Jackson, Cancer Control Agency of BC, 600 West 10th Avenue, Vancouver, BC, Canada V5Z 4E6.

3rd Congress of the European Society for Magnetic Resonance in Medicine and Biology
September 21–24, 1986
Aberdeen
Further details: Organising Secretary, Dr M. A. Foster, Department of Biomedical Physics, University of Aberdeen, Foresterhill, Aberdeen.

Blood Flow in the Brain
September 23–25, 1986
Strathclyde University, Glasgow
Further details Biological Engineering Society, Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN (Tel 01-242 7750).

Conference on the Interaction of Radiation Therapy and Chemotherapy
September 28–October 1, 1986
The Fort Magruder Inn, Williamsburg, Virginia
Further details. Ms Suzanne Bohn, American College of Radiology, 925 Chestnut Street, Philadelphia, PA 19107 USA (Tel. 215-574 3181).

Basic Review and Current Concepts in Neuroradiology and Head and Neck Radiology
A Harvard Medical School Postgraduate Course
September 29–October 3, 1986
Boston Marriott Hotel, Boston
Further details: Harvard Medical School, Dept of CME, Boston MA 02115, USA (Tel. 617-732 1525).

International Conference on Prostaglandin and Lipid Metabolism in Radiation Injury
October 1–3, 1986
Washington D.C.
Further details: Dr Thomas L. Walden, Biochemistry Department, Armed Forces Radiobiology Research Institute, Bethesda, Maryland 20814-5145 USA.

AER Symposium 1986 Tumours and Imaging
October 1–4, 1986
Vienna Hilton Hotel, Austria
Congress President: Prof. H. Pokieser, c/o Wiener Medizinische Akademie, Alser Strasse 4, A-1090 Wien, Austria (Tel. 222-421 383).

11th Annual San Diego Postgraduate Radiology Course
October 6–10, 1986
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San Diego Imaging Symposium
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November 12–14, 1986
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Chest Radiology
January 12–16, 1987
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Annual Update on Nuclear Radiology
January 16–18, 1987
San Diego, California
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(continued from outside back cover)

Page

Computed tomographic and pathological findings in pulmonary alveolar microlithiasis 407
A. G. Chalmers, J. Wyatt and P. J. Robinson

Psammomatous-like calcification in a Brenner tumour of the ovary 412
S. M. Schultz, T. S. Curry III and R. Voet

Intracranial Hodgkin's disease 414
P. R. Blake, D. H. Carr and A. W. G. Goolden

Case of the month

Haematuria: a red herring? 417
I. J. Kenney and I. G. Mackay

Short communications

3D positron emission tomography: preliminary results 419
R. J. Ott, J. E. Bateman, V. Batty, R. Clack, M. A. Flower, M. O. Leach, P. K. Marsden, V. R. McCready, S. Webb, H. Sharma and A. Smith

A Phase I study of the combined hypoxic cell radiosensitisers, Ro 03-8799 and SR 2508: a preliminary report of single-dose toxicity, pharmacokinetics and tumour concentrations 423
H. V. F. Newman, N. M. Bleehen and P. Workman

Correspondence

Field coverage in digital grey-scale fluorography of the chest 426
A. R. Cowen, J. M. Haywood and S. D. Morrison

Solitary thyroid nodule: what to do? 427
V. K. Kapoor, S. Kumar and L. K. Sharma

Scapular fracture 427
A. Banerjee

Book reviews

Induction of thyroid cancer by ionizing radiation. *NCRP* 316
Recent developments in digital imaging. *K. Doi, L. Lanzi and P.-J. P. Lin* (Eds) 316
Radiotherapy treatment planning, 2nd edit. *R. F. Mould* 354
Malignant tumours of the oral cavity. J. M. Henk and J. D. Langdon 354
Radionuclide imaging of the brain. *B. L. Holman* 358
Angiographic anatomy of the anterior inferior cerebellar artery. *J. J. Heimans, J. Valk and A. H. M. Lohman* 358
Cardiac imaging and image processing. *S. M. Collins and D. J. Skorton* (Eds) 364
A guide to cardiac ultrasound. *R. M. Donaldson and C. Westgate* 364
Practical radiotherapy planning. Royal Marsden Hospital practice. *J. Dobbs and A. Barrett* 372
The computation of dose distributions in electron beam radiotherapy. *A. E. Nahum* (Ed.) 372
Small cell lung cancer. *S. Seeber* (Ed.) 378
Lung cancer. Diagnostic procedures and therapeutic management with special reference to radiotherapy. *C. W. Scarantino* (Ed.) 378
Gynaecologic cancer. *A. A. Forastiere* 383
Liver cancer. *J. C. Bottino, R. W. Opfell and F. M. Muggia* (Eds) 384
Ovarian cancer. *C. N. Hudson* (Ed.) 384
CT densitometry in osteoporosis. *L. E. H. Lampmann, S. A. Duursma and J. H. J Ruys* 388
Clinical arthrography, 2nd edit. *R.-D. Arndt, J. W. Horne, R. H. Gold and D. D. Blaschke* 388
The Ionising Radiations Regulations 1985. *Health and Safety Commission, UK* 396
Assessment of radioactive contamination in man 1984. *International Atomic Energy Agency* 396
X-ray imaging equipment—an introduction. *E. Seeram* 428

BIR Bulletin and Calendar Events *facing page* 428

VOL 59 NO 700 APRIL 1986

The British Journal of Radiology

Contents

Page

Advances in technology and their impact on medicine: The Mackenzie Davidson Memorial Lecture, April 1986 309
A. R. Margulis and W. J. Shea Jr

Transcatheter embolisation of arterial aneurysms 317
R. Uflacker

Radionuclide venography: imaging monitor in deep-vein thrombosis of the pelvis and lower extremities 325
W. M. Sy and I. S. Seo

Intravenous digital subtraction angiography in patients with suspected bypass graft occlusion following surgery for peripheral vascular disease 329
P. Butler and B. Williamson

Metastatic deposits from a previously treated carcinoma of the lung presenting as a renal carcinoma 333
M. J. Bailey, J. E. Williams and P. R. Riddle

Mammographic changes following radiotherapy 337
J. H. Buckley and E. J. Roebuck

Precision of measurement of bone density with a special purpose computed tomography scanner 345
C. J. Hosie and D. A. S. Smith

The potential accuracy of dual-energy computed tomography for the determination of hepatic iron 351
R. G. Sephton

Correlation of human NMR T_1 values measured *in vivo* and brain water content 355
H. L. MacDonald, B. A. Bell, M. A. Smith, D. M. Kean, J. L. Tocher, R. H. B. Douglas, J. D. Miller and J. J. K. Best

Radiation doses and somatic risk to patients during cardiac radiological procedures 359
K. Faulkner, H. G. Love, J. K. Sweeney and R. A. Bardsley

A method for increasing the resolution of scanned projection radiography and other digital X-ray systems 365
D. R. Checkley, X. P. Zhu, D. S. Hickey, J. K. Hughes, J. B. Carter and I. Isherwood

Report of a randomised pilot study of the treatment of patients with supratentorial gliomas using neutron irradiation 373
W. Duncan, J. McLelland, W. J. L. Jack, S. J. Arnott, A. Gordon, G. R. Kerr and J. R. Williams

The results of a randomised trial of mixed-schedule (neutron/photon) irradiation in the treatment of supratentorial Grade III and Grade IV astrocytoma 379
W. Duncan, J. McLelland, W. J. L. Jack, S. J. Arnott, P. Davey, A. Gordon, G. R. Kerr and J. R. Williams

Radioiodine treatment of solitary functioning thyroid nodules 385
G. E. Ratcliffe, S. Cooke, I. Fogelman and M. N. Maisey

The radiosensitivity of microcolony- and macrocolony-forming cells in mouse tail epidermis 389
F. Chen and J. H. Hendry

Technical note

A modified Selectron vaginal applicator 397
R. Thomas, G. A. Corner and E. R. Watson

Case reports

Synovial chondromatosis of the hip joint presenting as a pathological fracture 399
P. Szypryt, P. Twining, B. J. Preston and C. J. Howell

Mycotic aneurysm of the renal artery: CT appearance 401
J. M. Stavas, D. B. Reinke and R. P. Miller

Diagnosis of spontaneous aorto-caval fistula by computed tomography 403
R. Clements, E. Fitzgerald and A. Thorpe

Calcified gastric cancer: report of a case and review of the literature 405
A. Rotondo, R. Grassi, F. Smaltino, A. Greco, A. W. L. Leung and D. J. Allison

(*continued on inside back cover*)

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Volume 59 Number 7
May 198

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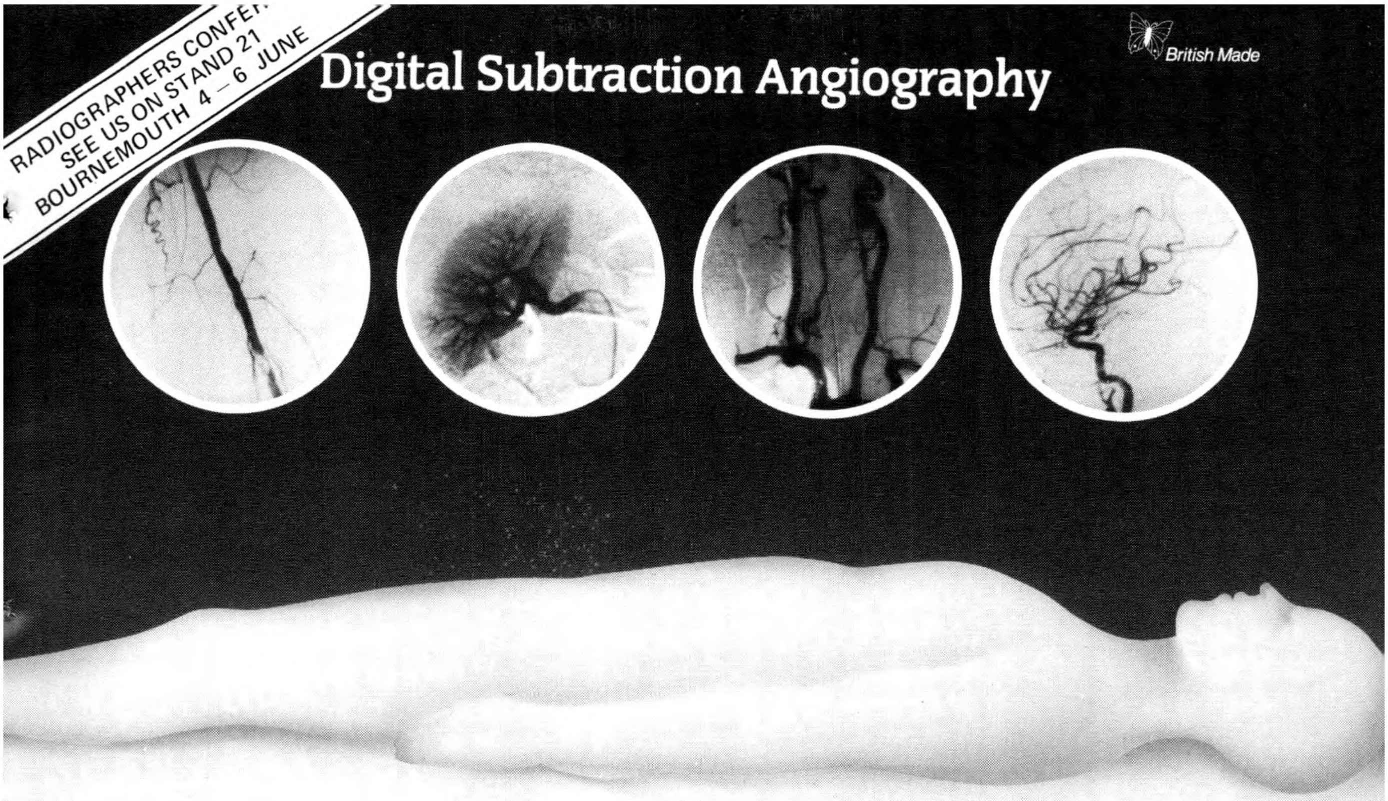

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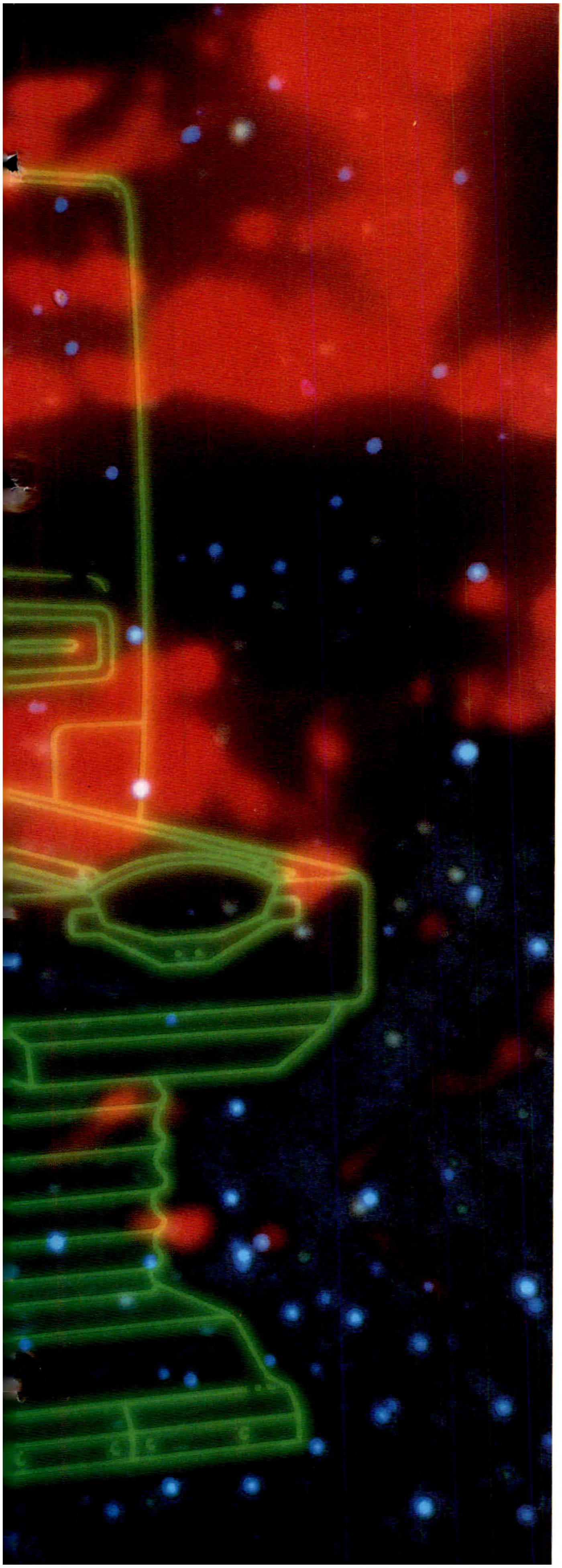

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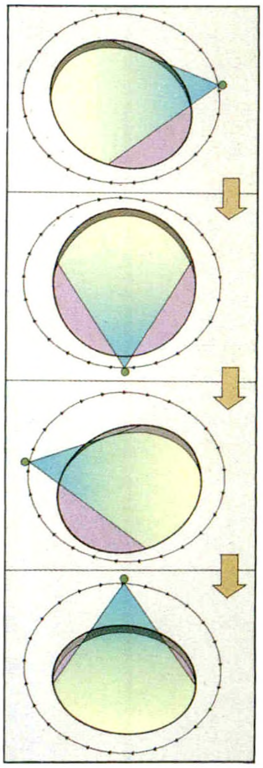

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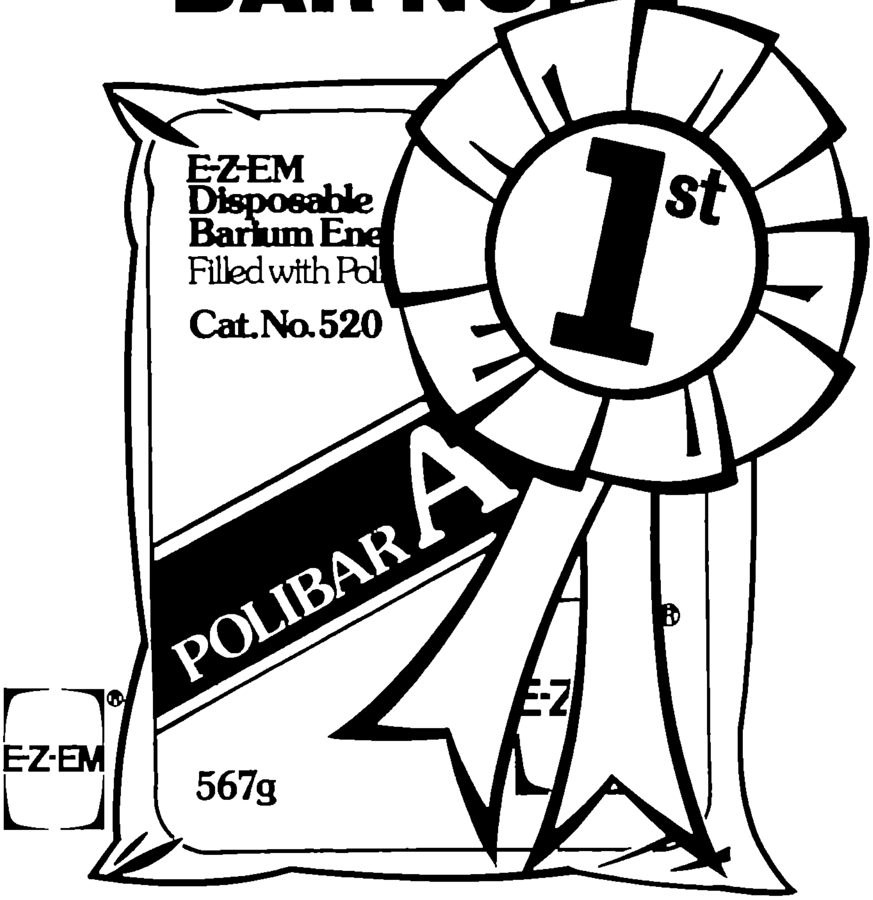

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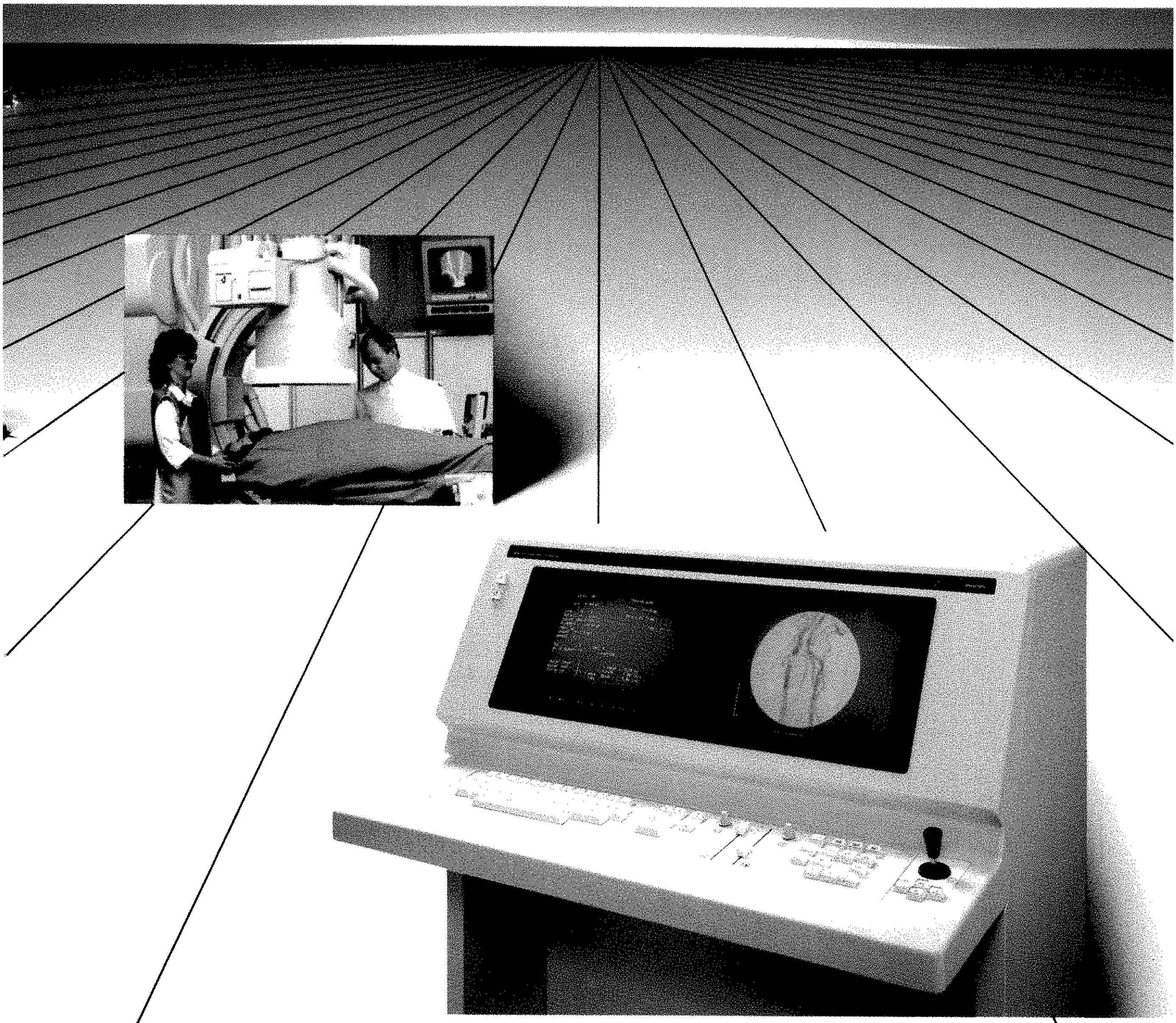

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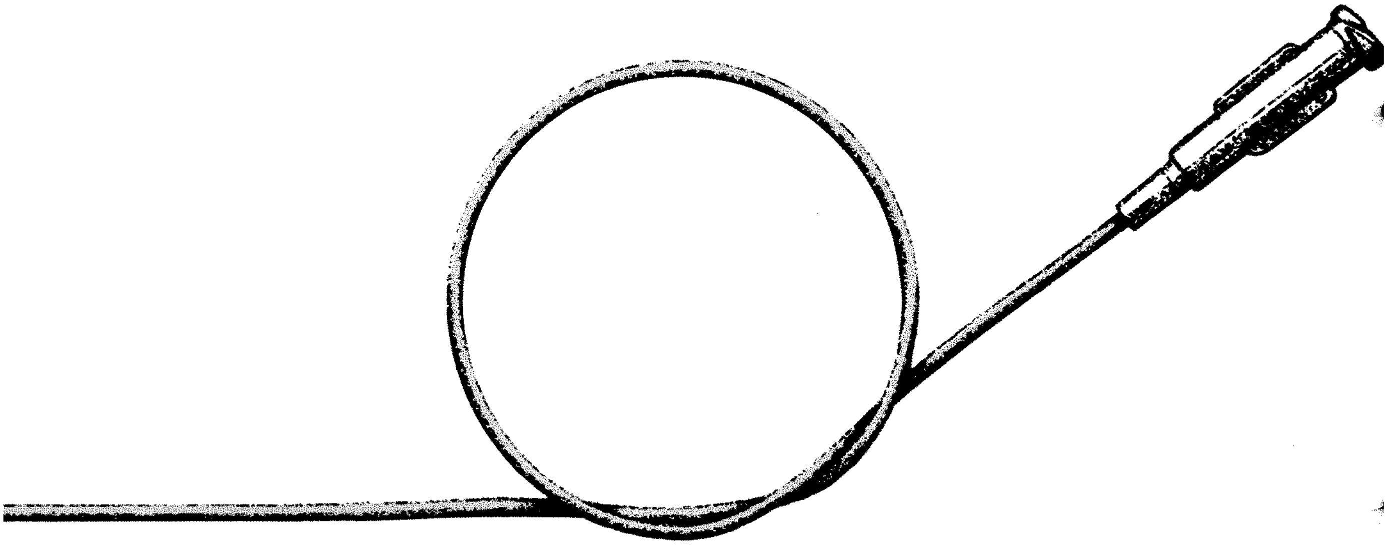

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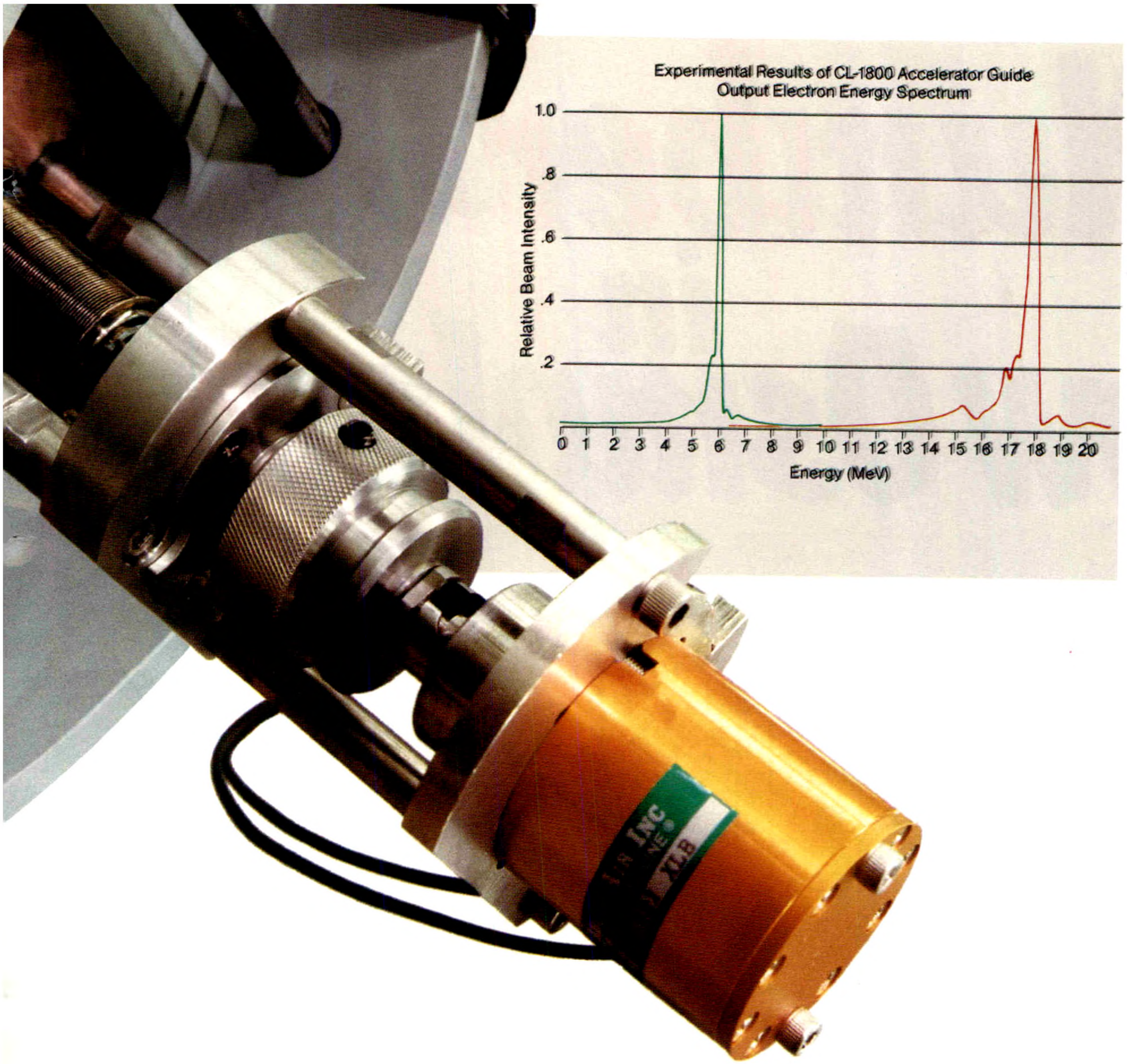

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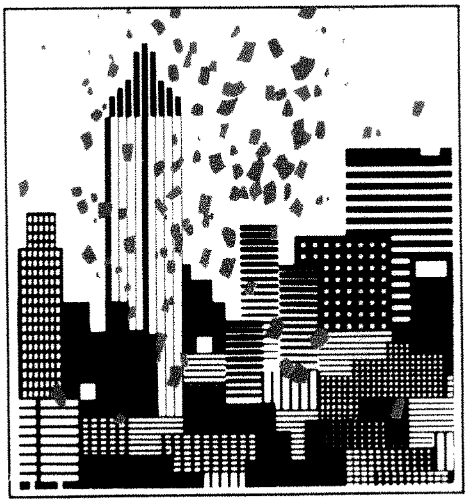

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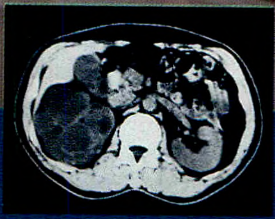

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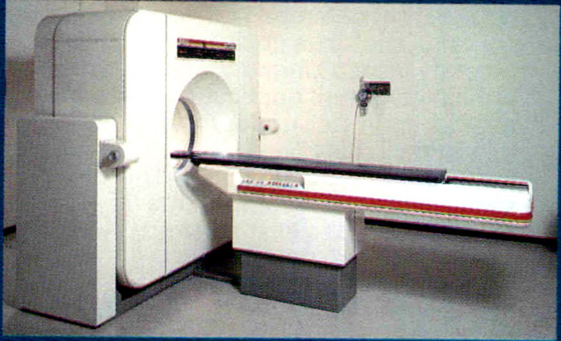

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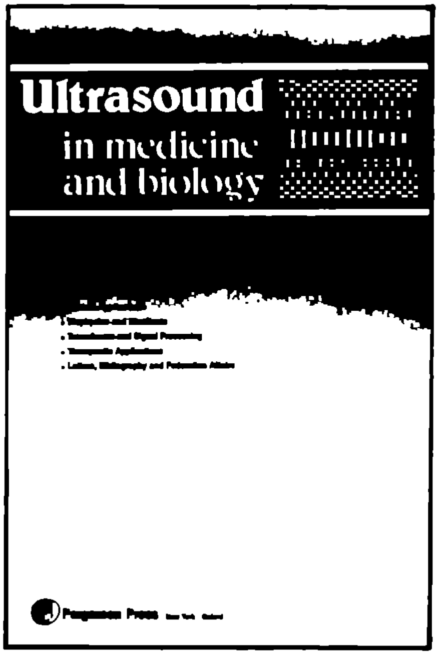

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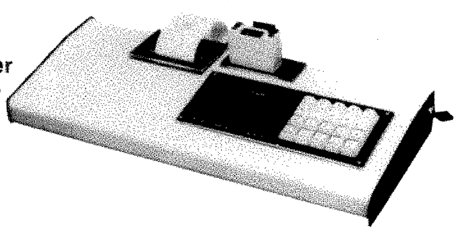

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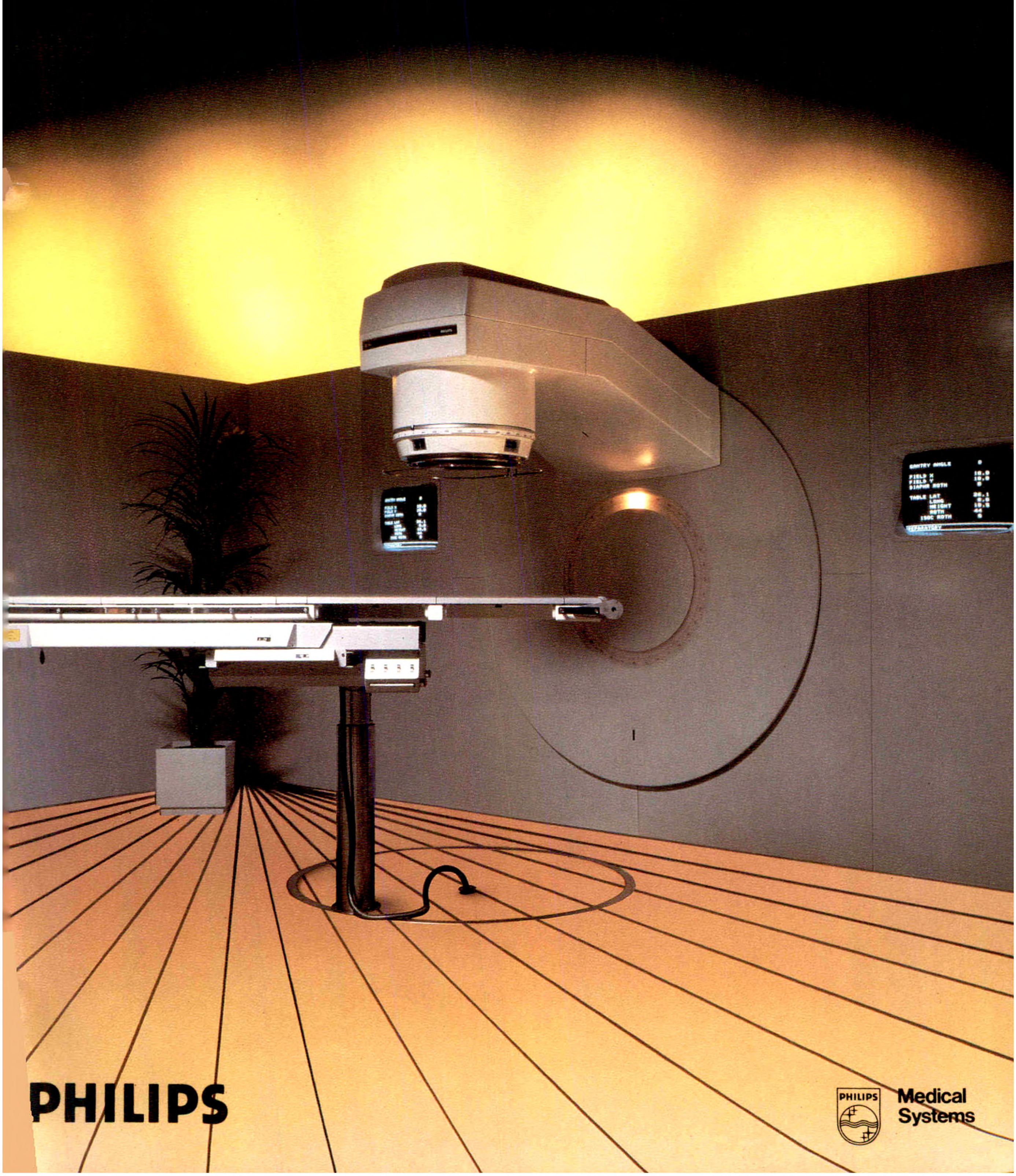

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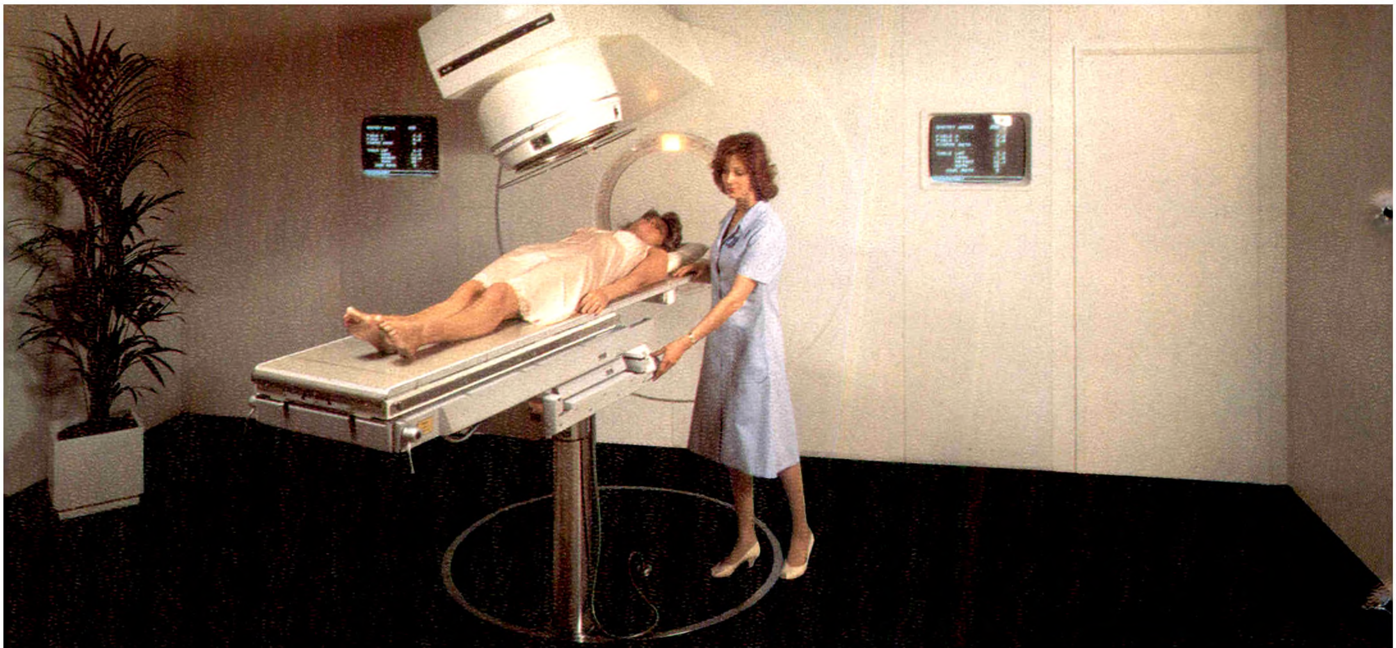

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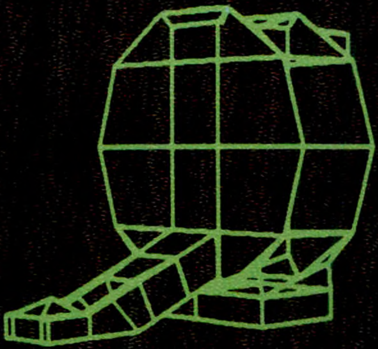

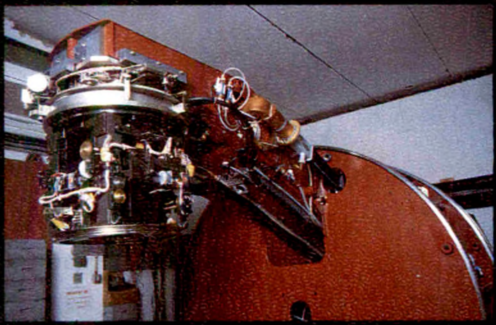

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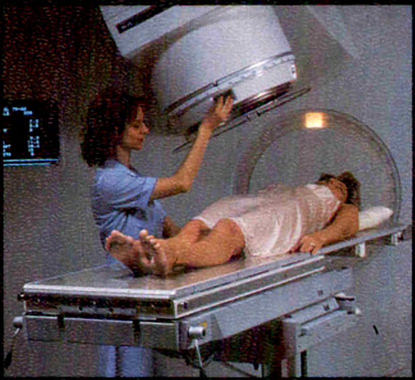

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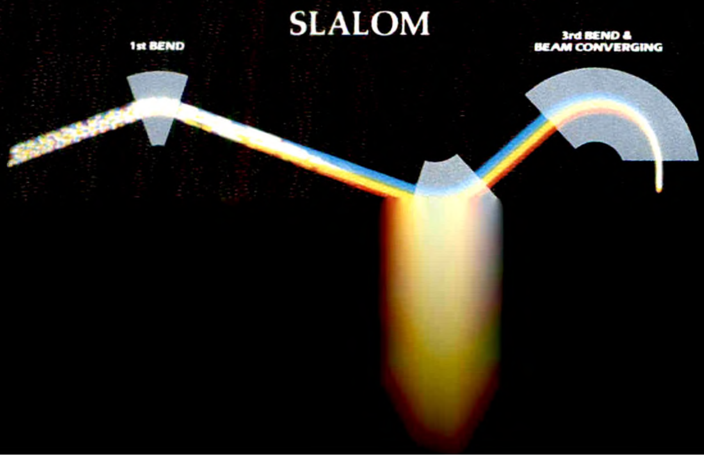

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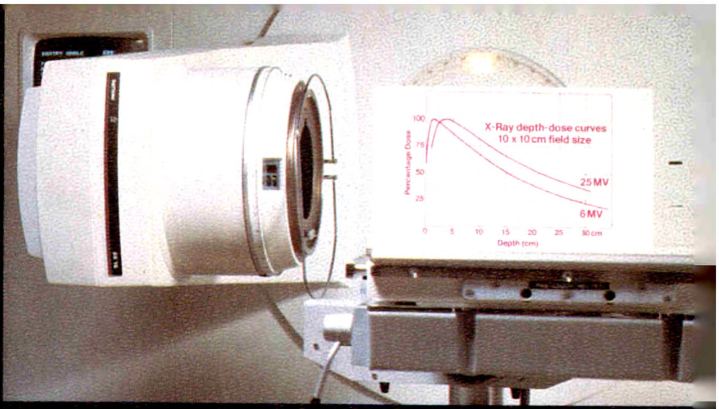

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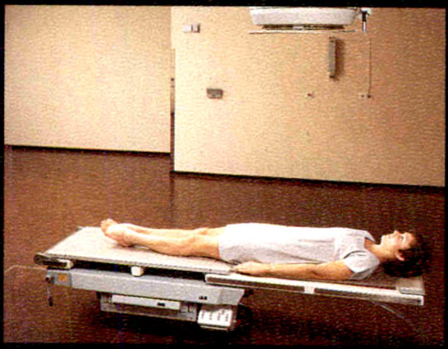

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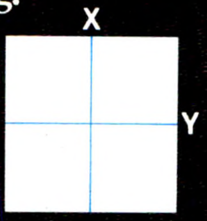

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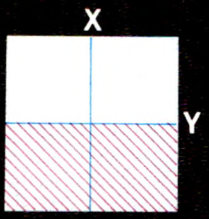

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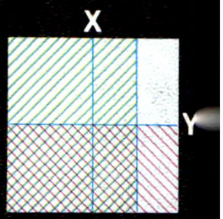

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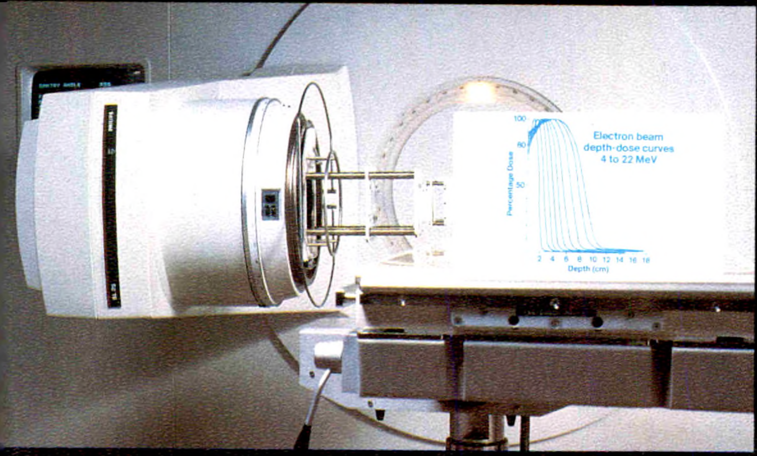

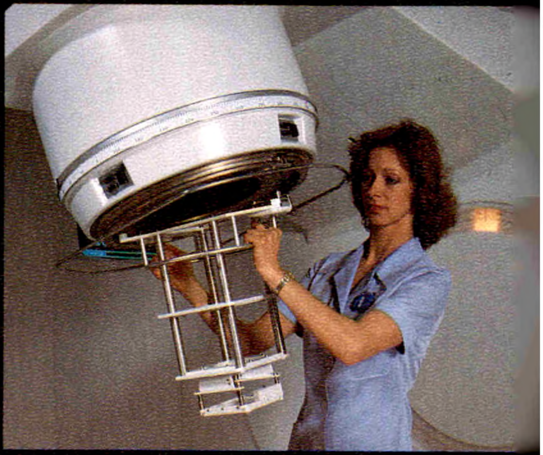

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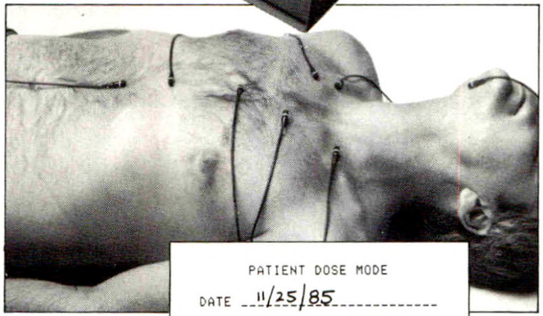

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The British Journal of Radiology

A comparative review of the Hammersmith (1971–75) and Edinburgh (1977–82) neutron therapy trials of certain cancers of the oral cavity, oropharynx, larynx and hypopharynx*

Medical Research Council Neutron Therapy Working Group†

(*Received October 1985 and in revised form December 1985*)

ABSTRACT

Because of apparent inconsistencies in the two trials of neutron therapy carried out under its auspices, the MRC in 1982 requested a comparative review of the data in the Hammersmith and Edinburgh trials in so far as the clinical material allowed of such comparison.

It was clear that the two trials were not only not contemporaneous (Hammersmith 1971–75; Edinburgh 1977–82) but that they differed in site and stage of disease as well as in the parameters of radiation dosage. Only a fraction of the patients were comparable and this review, which sets out the differences in design and conduct of the two trials, focuses on squamous-cell carcinoma in the four sites—oral cavity, oropharynx, larynx and hypopharynx—which were common to both. The first 120 patients entered into the Edinburgh trial have been compared with the 95 patients selected from the 161 in the Hammersmith trial who would have been eligible at Edinburgh by reason of the site of disease and histology. Thus, Hammersmith patients with tumours of salivary glands, sinuses and neck nodes were, of necessity, excluded. Within such limitations the data on case distribution, tumour size and stage, the parameters of radiation dosage and the outcome in terms of tumour control, survival and treatment morbidity have been subjected to rigorous assessment and analysis. The important aspects in which the two investigations had differed included the stage of disease (more advanced at Hammersmith, with 63% of patients having fixed nodes, compared with 27% at Edinburgh), radiation dosage (the median *neutron* dose being 5% lower at Edinburgh than at Hammersmith while the median *photon* dose was 10% higher at Edinburgh); the "photon arm" of the Edinburgh trial being on site whereas that at Hammersmith had been at multiple centres; and the years in which the trials had been carried out.

The two series are comparable in terms of treatment failure (local recurrence or late radiation death) following local tumour control. The results are also consistent in associating an increased incidence of late severe radiation morbidity and of intercurrent deaths with neutron therapy. In three other respects the results of the two series differ. At Edinburgh there was advantage to the photon-treated patients in terms of overall mortality, whereas at Hammersmith the advantage was to those treated with neutrons. The incidence of tumour regression for patients randomised to photons was much lower in the Hammersmith trial than for neutrons, whereas in Edinburgh the two modalities gave similar results. The recurrence rate for patients treated by neutrons at Hammersmith was very low compared with that recorded for those treated by photons, and this difference was not observed in the Edinburgh series. In discussing these results it must be borne in mind that the numbers of cases in individual categories were small, and the low power of multiple significance tests means that only large differences, both real and fortuitous, achieve statistical significance and moderate effects go unremarked. While the higher radiation-related mortality which was associated with higher neutron doses delivered tended to offset the lower recurrence rate observed at Hammersmith, the extent to which morbidity was related to poor penetration and uneven dose distribution from the neutron beams available remained incompletely defined.

The findings in this restricted group of squamous cancer are, in fact, consonant with those from a multi-centre controlled trial carried out at Edinburgh, Amsterdam and Essen and reported by Duncan et al (1984). On the other hand, the restricted group analysed represents only 3% of patients treated with neutrons at Hammersmith, from where beneficial results have been reported (Catterall, 1981; Catterall et al, 1984) in other head and neck tumours, for example in "Phase 2" studies of malignant tumours of salivary glands and of the facial area including sinuses.

The present study has compared the use of a poorly understood quality of radiation generated by inadequate equipment with standard megavoltage X irradiation, and general conclusions about the value of neutron therapy cannot be drawn from this limited review. A full appraisal of its place, both for certain stages of specifically selected tumours and in the context of general clinical oncology, will have to await the outcome of a new generation of trials now being planned which will utilise machines producing higher-energy neutrons

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*Report to the MRC Cell Biology and Disorders Board of an *ad hoc* Working Group on Neutron Therapy, May 1985

†*Membership*: Professor A. E. Jones (Chairman), Dr D. K. Bewley, Dr Mary Catterall, Professor W. Duncan, Dr Sheila M. Gore (from October 1982), Miss Gillian R. Kerr, Dr I. Sutherland (until October 1982), Mr D. D. Vonberg and Mr J. R. Williams

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Design of the Trials

The principal criteria for admission to the two trials are given in Table I. Important differences in the selection of patients concern the type of lesion, the pathology, tumour site and stage. In Edinburgh, the patients randomised included those with earlier cancers. The Hammersmith trial was a multicentre one and patients randomised to photon therapy could be treated and followed up at the referring radiotherapy centre, using whatever dose/fractionation scheme was considered to be appropriate. At Edinburgh, all patients were treated at the Western General Hospital using the same fractionation and overall treatment times for both photons and neutrons.

In each trial, a method of balanced randomisation, taking account of prognostic factors, was followed. Regarding follow-up assessment, the protocol for the Edinburgh trial specified uniform follow-up, whilst in the Hammersmith trial there was no uniform surveillance policy.

Patient data

This review compares the first 120 patients entered into the Edinburgh trial with the 95 patients selected from the 161 in the Hammersmith trial who would have been eligible at Edinburgh by reason of the site of disease and histology. In the Edinburgh trial there were 60 patients treated by photons and 60 by neutrons and in the Hammersmith trial, 44 treated by photons and 51 by neutrons. For the purpose of this review the Hammersmith patients have been reclassified according to the UICC (1974) TNM system. Patients from Edinburgh had a minimum follow-up of 6 months. Assessment of morbidity was subsequently updated to 12 months.

The distribution of patients by tumour site (Table II) is broadly similar between the two centres, 57% of Edinburgh patients having tumours of the oral cavity or oropharynx compared with 69% in the Hammersmith review series. The

TABLE I

Comparative features of two trials

	Hammersmith 1971–75	Edinburgh 1977–82
Site of cancer	Oral cavity Oropharynx Larynx Hypopharynx	Oral cavity Oropharynx Larynx Hypopharynx
	Nasopharynx Maxillary antrum Salivary glands Cervical oesophagus Secondary neck nodes	
Treatment state	(A) Primary cancers (i) previously untreated (ii) recurrent after surgery (B) Secondary neck nodes (i) primary not known (ii) primary successfully treated	(A) Primary cancers (i) previously untreated
Histology	All malignant tumours except lymphoma and lymphoepithelioma	Squamous-cell carcinoma
Stage	UICC (1968)	UICC (1974)
	All stages *except* T_1+T_2/N_0	All stages *except* T_1, N_0 oral cavity, oropharynx and larynx T_2, N_0 glottis and tongue (if suitable for implant)
	M_0	M_0
Age and sex	< 85 years Both males and females	< 80 years Both males and females
Radiation beams used	Neutrons: from 16 MeV d on Be/Cu Photons: 4–10 MV X rays and ^{60}Co gamma rays	Neutrons: from 15 MeV d on Be Photons 4 MV X rays

TABLE II

Distribution of tumours by site

	Edinburgh		Hammersmith	
	Neutrons	Photons	Neutrons	Photons
Oral cavity	20	26	22	17
Oropharynx	14	8	15	12
Larynx	18	17	9	11
Hypopharynx	8	9	5	4
Total	60	60	51	44

TABLE III

DISTRIBUTION BY T AND N CLASSIFICATION

Stage	Edinburgh		Hammersmith	
	Neutrons	Photons	Neutrons	Photons
T_1	0	1	0	0
T_2	15	16	2	4
T_3	39	35	37	32
T_4	6	8	12	8
N_0	34	31	11	12
N_1	8	13	3	5
N_2	0	2	1	3
N_3	18	14	36	24
Total	60	60	51	44

overall distribution of T and N classifications is given in Table III. It will be seen that the Hammersmith patients had significantly more advanced disease in respect both of the "T" stage and the "N" stage. Sixty-three per cent of the Hammersmith patients had fixed nodes compared with 27% at Edinburgh. The modified Karnofsky index was used at Edinburgh, where all patients were graded 1, 2 or 3, but not in the Hammersmith trial. The Hammersmith trial had many patients who, being in poor general condition, probably exceeded Grade 3.

Since the numbers of patients in some T and N classifications are very small, the T and N stages have been combined to form a new variable "level of severity" which can take the values 1, 2 or 3 as shown in Table IV. All analyses concerning the severity of disease are in terms of this variable. The distribution of patients by level of disease severity is given in Table V. Whereas 54% of Edinburgh patients had Level of Severity 1, 60% of Hammersmith patients were Level 3.

TABLE IV

LEVEL OF SEVERITY BY T AND N CLASSIFICATION (NO. OF PATIENTS IN PARENTHESES)

	N_0	N_1	N_2	N_3
T_1	**1** (0)	**1** (0)	**1** (0)	**2** (1)
T_2	**1** (18)	**1** (10)	**2** (1)	**2** (8)
T_3	**1** (55)	**2** (14)	**2** (5)	**3** (69)
T_4	**2** (15)	**2** (5)	**3** (0)	**3** (14)

TABLE V

DISTRIBUTION OF PATIENTS BY DISEASE SEVERITY

Level of severity	Edinburgh		Hammersmith	
	Neutrons	Photons	Neutrons	Photons
1	33	32	7	11
2	12	17	9	11
3	15	11	35	22
Total	60	60	51	44

Patients in the two centres were similar in terms of age (mean 63.7 years, SD ± 10.0 years) and sex apart from there being fewer than expected male patients randomised to receive photon therapy at Edinburgh (Edinburgh: photons 32 out of 60 were male, neutrons 46 out of 60 were male).

Radiotherapy: energies, dosages and treated volumes

The treatment energies used are shown in Table I. The Hammersmith and Edinburgh cyclotrons were of similar energy, but gave neutron beams which were much less penetrating than the photon beams used for the control patients. The neutron beams at both centres were obtained by a number of interchangeable collimators. The Edinburgh machine was fitted with a movable head whereas the Hammersmith beam was fixed in the horizontal position.

To compare the clinical results in the two trials it is necessary that the statement of dose at each centre should be consistent. Therefore, for this intercomparison the recommendations of ICRU Report 29 (ICRU, 1978) have been followed. The absorbed dose at the centre of the treatment volume has been calculated for each patient.

Neutron treatments were given three times weekly at Hammersmith and five times weekly at Edinburgh over a 4-week period in both centres. At Hammersmith, 43% of patients received a neutron dose between 1500 cGy and 1600 cGy, with five patients (10%) receiving a lower dose and the remaining 47% receiving more than 1600 cGy. In Edinburgh, 68% of patients received a neutron dose within this range, with only one patient receiving a higher dose and the remaining patients (30%) receiving less than 1500 cGy. The contribution of gamma rays, 5–9% of the total dose, has been ignored. The typical dose per fraction was 1.30 Gy at Hammersmith and 0.80 Gy at Edinburgh. A standardised neutron dose has been obtained by allowing for the total treatment time, using the factor $T^{0.11}$ and normalising to 28 days. No account has been taken of the number of fractions. The median standardised central dose of neutrons was 15.24 Gy at Edinburgh and 15.95 Gy at Hammersmith.

For the photon-treated patients in Edinburgh the protocol specified that the dose should be delivered in 20 fractions over 4 weeks, although, in fact, four patients each had 18, 19, 21 and 22 fractions. The Hammersmith trial protocol allowed the institute at which the patient was treated to use the dose and fractionation scheme which would normally be used there. The TDF system has therefore been used (Orton & Ellis, 1973) to standardise photon doses. No Edinburgh patient had a time dose factor less than 93 and the median TDF was 107. For part of the data analysis a dose restriction was applied which excluded those patients whose TDF was less than 93; this corresponds to a dose of 50 Gy in 20 fractions over 4 weeks. When the 20 photon-treated patients whose TDF was unkown or less than 93 are excluded, the median TDF for Hammersmith photon patients is 107, as in the Edinburgh series. Maximum normal tissue doses were also recorded. These were standardised for both neutrons and photons in the same way as central neutron dose.

There were differences in treatment technique at the two centres. At Edinburgh, wedge filters were extensively used with the neutron beam to compensate for irregularities of surface anatomy. At Hammersmith this was done with bolus; wedge-filters were used only for non-opposed fields. For neutron patients at Hammersmith bolus was lined with lead to reduce early skin reactions. Beam direction shells were used with nearly all patients at both centres. At Hammersmith neutron patients were treated in the sitting position as the beam was horizontal, whereas at Edinburgh the isocentric unit allowed patients to be treated supine

Field sizes were larger at Hammersmith than at Edinburgh, corresponding to the more advanced tumours treated. Median values when two fields were used were 54 cm² (Ed. P), 49 cm² (Ed N), 80 cm² (HP) and 90 cm² (HN) When three fields were used with neutrons at Edinburgh the median field size was 72 cm² (see Table VI).

Analysis methods

Pathways charting the progress of the treated disease for the patients in each trial are shown in Fig. 1.

Three comparisons take the date of first treatment as their starting point, that is, overall mortality, time to becoming locally well and time to death, never having been locally well. Other comparisons, which apply to those patients who had complete regression of all local disease, are taken from the date at which the patient was observed to be locally well or from the date of recurrence.

One analysis strategy, proportional hazards (Cox, 1972), has been used throughout. This assumes, for overall mortality, a baseline pattern over time for the risk of dying. This baseline hazard is multiplied up or down by the exponential of a risk score which is derived as a weighted sum of patient covariates. The covariates, or explanatory variables, which were accounted for simultaneously are: site (oral cavity, oropharynx, larynx versus baseline, hypopharynx); age (65 years or less versus the baseline, age over 65 years), disease severity (Severity 2, Severity 3 versus baseline, Severity 1); trial (Edinburgh versus baseline, Hammersmith); treatment (neutron therapy versus baseline, photon therapy).

Two regression models are compared at each analysis. In Model A, one neutron effect (common to both trials) is estimated, while in Model B we allow separate neutron effects to be estimated for the two trials. The test statistic for comparing Models A and B is distributed approximately as chi-squared with one degree of freedom. Large values of this test statistic indicate a treatment by trial interaction, that is, the neutron effect is different in the Edinburgh and Hammersmith trials. The proportional hazards analysis (Model A) is equivalent to a log-rank analysis of neutron therapy versus photon therapy controlling for site of tumour, age, disease severity and trial.

For simplicity, ordinary life-tables are shown without adjustment for covariates but their formal comparison is based always on the proportional hazards (log-rank) analysis.

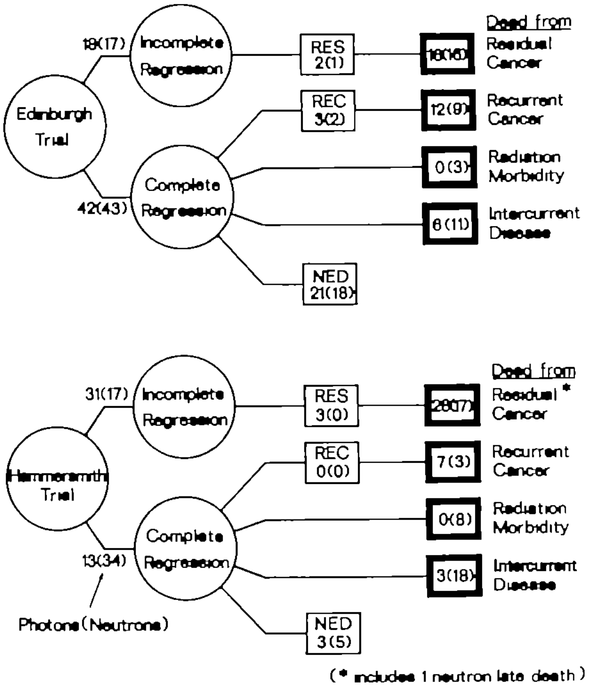

FIG. 1.

Flow charts showing the possible pathways of the progress of the treated disease. The numbers of patients who pass between two different states are shown for each pathway, as well as the numbers who remain in each state. In each case the number of photon-treated patients precedes the number of neutron-treated patients

TABLE VI

AVERAGE FIELD SIZE (CM²)*

	Edinburgh		Hammersmith	
	Neutrons	Photons	Neutrons	Photons
No of fields: 2				
Minimum	36	28	48	25
Median	49	54	90	80
Maximum	176	121	239	324
No assessed	37	56	50	39
Missing values				1
No of fields: 3				
Minimum	35	35		
Median	72	72	82	60
Maximum	176	108		
No. assessed	23	3	1	1
Missing values		1		

*In addition, field sizes were 35 cm² and 84 cm² for two Hammersmith photon-treated patients who had one treatment field only.

RESULTS

Tables VII and VIII are a schematic summary of the interrelated analyses on the data for all 215 patients. Explanatory variables which make a significant contribution to a particular risk score are annotated √ if the prognosis is favourable to the patient, or × if detrimental. Regression coefficients which differ significantly from zero are those for which the corresponding absolute *t*-value exceeds 2 (5% level), 2.3 (2% level), 2.6 (1% level) and so on. The problems of multiple significance testing should be borne in mind. *The low power of the tests means that only large differences, both real and fortuitous, achieve statistical significance and moderate effects go unremarked.*

TABLE VII

SUMMARY OF ANALYSIS: EXPLANATORY VARIABLES AND TREATMENT EFFECTS (215 PATIENTS)

	(1) Overall mortality (157 deaths)	(2) Time to becoming locally well (132 locally well)	(3) Time to death, never having been locally well (77 deaths)
Explanatory variables			
Oral cavity			
Oropharynx	√		
Larynx	√	√√√	
Age 65 years or less	√√	×	√
Severity 2	×××	×××	
Severity 3	×××	×	××
Regression coefficients (|t| value): treatment and trial effects			
(A) Common neutron effect	−0.01 (0.06)	0.40 (2.23)	−0.31 (1.24)
Edinburgh trial	−0.04 (0.25)	0.69 (3.35)	0.27 (1.07)
(B) Edinburgh neutron effect	0.45 (1.87)	0.12 (0.54)	−0.02 (0.07)
Hammersmith neutron effect	−0.45 (1.92)	0.98 (2.95)	−0.51 (1.60)
Edinburgh trial	−0.50 (2.05)	1.20 (3.67)	0.05 (0.15)
Model preference	B	B	A
χ_1^2	7.18, $p < 0.01$	4.94, $p \sim 0.03$	1.06 (NS)

× or √, $0.10 > p > 0.05$.
×× or √√, $0.05 > p > 0.01$.
××× or √√√, $0.01 > p$.

TABLE VIII

SUMMARY OF ANALYSIS OF RECURRENCE AND DEATH AFTER BECOMING LOCALLY WELL: EXPLANATORY VARIABLES AND TREATMENT EFFECTS (132 PATIENTS)

	Time from locally well to: (1) recurrence (36 events)	(2) death without recurrence (49 events)	(3) recurrence or late radiation death (47 events)	(4) intercurrent death (38 events)	(5) death (80 events)	(5) time from recurrence to death (31 events)
Explanatory variables						
Oral cavity				√√	√	*
Oropharynx						*
Larynx						*
Age 65 years or less		√√√		√√	√√	*
Severity 2	××		×			
Severity 3	××	×××	×××	×××	×××	×
Regression coefficients (|t| values): treatment and trial effects						
(A) Common neutron effect	−0.59 (1.63)	1.21 (3.06)	−0.08 (0.25)	0.75 (2.93)	0.52 (2.01)	0.64 (1.56)
Edinburgh trial	−0.64 (1.42)	0.10 (0.27)	−0.32 (0.90)	1.70 (5.14)	0.15 (0.55)	−1.16 (2.43)
(B) Edinburgh neutron effect	−0.05 (0.13)	1.26 (2.51)	−0.47 (0.91)	0.79 (2.72)	0.77 (2.37)	0.34 (0.75)
Hammersmith neutron effect	−1.99 (2.78)	1.14 (1.77)	0.13 (0.34)	0.62 (1.23)	0.10 (0.25)	1.75 (2.23)
Edinburgh trial	−0.22 (0.42)	0.01 (0.01)	−0.03 (0.06)	1.58 (3.05)	−0.27 (0.65)	−0.87 (1.67)
Model preference	B	A	A	A	A	A
χ_1^2	5.86 $p \sim 0.02$	0.02	0.86	0.08	1.58	2.30

*Not fitted.
× or √, $0.10 > p > 0.05$.
×× or √√, $0.05 > p > 0.01$.
××× or √√√, $0.01 > p$.

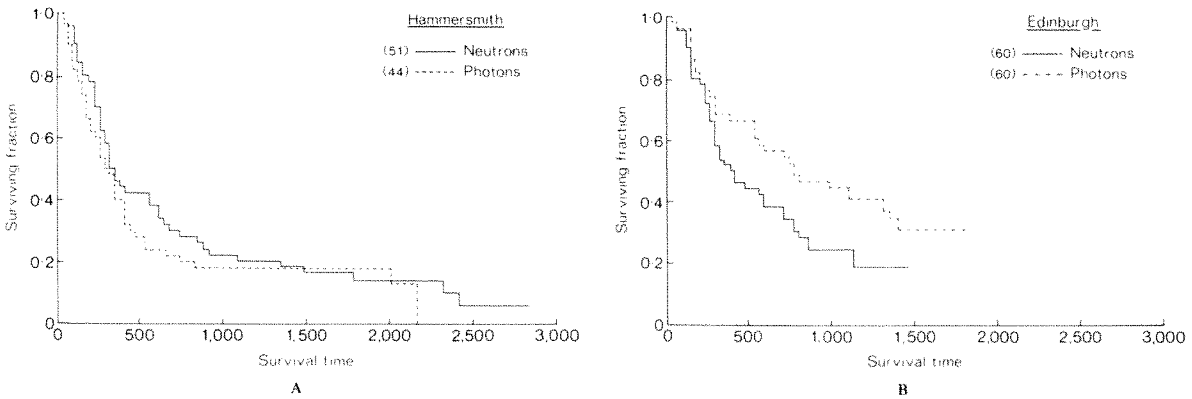

FIG. 2.

(A, B) Actuarial survival curves for the patients in the two trials. These curves are not adjusted for the effects of age, site and severity of disease. The poor survival in the Hammersmith trial is associated with the more advanced disease of the patients. (Hammersmith 60% disease Severity 3, Edinburgh 22% disease Severity 3).

Overall mortality, local tumour control and overall treatment failure

At Edinburgh, 34 out of 60 patients treated with photons have died, as have 39 of the 60 patients treated with neutrons. At Hammersmith, follow-up has been longer: 38 out of 44 photon-treated patients have died together with 46 of the 51 neutron-treated patients. Life tables are shown in Fig. 2. Comparison of mortality, taking account of the explanatory variables, is made in Table VII for neutron- and photon-treated patients within each trial (Model B) and by assuming a common neutron effect between trials (Model A). The data from the two trials are combined to estimate regression coefficients for the prognostic factors tumour site, age and severity. In terms of overall mortality, the effect of neutron versus photon therapy is significantly different in the two trials ($\chi_1^2 = 7.18$, $p < 0.01$). The mortality rate is greater after neutron therapy in Edinburgh than after photon therapy, but the reverse is true in the Hammersmith series.

At Edinburgh, local tumour control was achieved in 42 out of 60 photon-treated patients and in 43 out of 60 patients treated with neutrons. The data are consistent with there being no difference in time to local tumour control between the two groups. In the Hammersmith trial, 13 out of 44 photon-treated patients became locally well compared with 34 out of 51 neutron-treated patients. Table VII confirms that, in terms of time to complete regression, the results of the two series are significantly different ($\chi_1^2 = 4.94$ $p \sim 0.03$). Complete regression of tumour was achieved more often in neutron-treated patients than in those treated by photons in the Hammersmith series.

The fate of those who never became locally well was similar in the two trials (Table VII, Column 3). Overall treatment failure (defined as death, never being locally well, recurrence of local disease or late radiation mortality) occurred in 28 out of 60 (47%) photon-treated patients and 28 out of 60 (47%) neutron-treated patients in the Edinburgh trial. In the Hammersmith trial treatment failed overall in 35 out of 44 (80%) photon-treated patients and in 28 out of 51 (55%) neutron-treated patients.

The differing effect of neutrons on overall mortality in the two trials which has been observed could be a guise for some other effect, such as a differential effect of disease severity. If neutron therapy were superior for more advanced tumours of the oral cavity, oropharynx, larynx and hypopharynx and photon therapy were better for patients with limited disease, then because 60% of the Hammersmith trial patients had Severity 3 disease compared with only 22% of the Edinburgh patients, a differential effect of disease severity on the value of neutron therapy might appear as a differential effect of the centre at which the tseatments were given. Two series of models, which focus respectively on risk score and severity, were, therefore, fitted to elucidate this possibility. We note, however, that 215 patients are too few, by a factor of four, reliably to discover moderate main effects of treatment, let alone to chase interactions with other factors.

The regression coefficients for overall mortality associated with tumour site, severity and age of the patient have been used to compute partial risk scores. The second series of models focuses on disease severity (coded 1, 2 and 3) to obviate criticism about circularity in re-use of the risk score for the same data from which it was derived.

The two series of models are summarised in Table XII: Model 1 fits only main effects, Model 2 adds treatment by risk score or severity interaction, which allows a differential treatment effect according to risk score or disease severity, Model 3 adds instead treatment by trial interaction and Model 4 adds both.

We note that treatment by risk score interaction is

TABLE IX

SCORING SYSTEMS FOR LATE NORMAL TISSUE MORBIDITY

	Score 1	Score 2	Score 3	Score 4
Skin	Slight atrophy	Moderate telangiectasia	Marked telangiectasia	(a) Superficial ulceration < 50% treated area (b) Deep ulceration or superficial ulceration > 50% treated area
Subcutaneous tissue	Slight induration	Asymptomatic fibrosis with < 10% linear contraction	Marked fibrosis with > 10% linear contraction	Symptomatic fibrosis
Larynx	Asymptomatic oedema of arytenoids	Symptoms due to oedema, telangiectasia or early fibrosis	Fibrosis of cords, chondritis	Necrosis
Mucous membrane	Slight telangiectasia, some dryness, slight atrophy, loss of taste	Moderate telangiectasia, moderate dryness	Marked telangiectasia, complete dryness	(a) Superficial ulceration > 50% treated area (b) Deep ulceration
Salivary glands	Fibrosis, no dryness of mouth	Normal diet possible with added fluids	Symptomatic dryness, semisolid food required	Complete dryness

Note: Score 0, no observed change; Score 5, death directly related to radiation complication.

almost as marked as the treatment by trial interaction (1 vs 2 compared with 1 vs 3). Comparison of risk score Models 1 and 4 leads to a chi-squared statistic on two degrees of freedom ($\chi_2^2 = 10.88$) which, being significant at the 1% level, admits of two interactions; comparison of risk score Models 3 and 4 leads to a chi-squared statistic on one degree of freedom ($\chi_1^2 = 3.54$) which is significant only at the 6% level. There is, thus, marginal support for the treatment by risk score interaction over and above the noted treatment by trial interaction, that is reduced mortality after neutron therapy for patients with the worst prognosis. In the second series, support for treatment by disease severity interaction in addition to treatment by trial interaction is much weaker ($\chi_1^2 = 0.80$).

Recurrence and death after becoming locally well

Characteristics of patients achieving local tumour control may differ between the forms of treatment. Regression analysis adjusts for imbalances in known prognostic factors between patients who became locally well on neutron and photon therapy but estimated treatment effects still do not carry a randomisation guarantee.

Thirty-six patients developed local recurrence of disease after becoming locally well: 15 out of 42 patients treated with photons and 11 out of 43 patients treated with neutrons at Edinburgh and, in the Hammersmith trial, seven out of 13 photon patients but only three out of 34 neutron patients. The time-specific risk of recurrence was significantly lower for patients in the Hammersmith trial treated with neutrons rather than photons, whereas in the Edinburgh trial there was no such marked treatment differential ($\chi_1^2 = 5.86$, $p \sim 0.02$; see Table VIII, Column 1).

There were no late radiation deaths after photon therapy but amongst the 77 neutron-treated patients who became locally well, 11 such deaths occurred, eight in the Hammersmith series. If both recurrence and death from treatment morbidity are considered as treatment failures, there is no significant difference between neutron and photon therapy in either trial or in the two trials combined, for those who have become locally well (Table VIII, Column 3, Model A).

Six out of 42 Edinburgh photon-treated patients and 11 out of 43 Edinburgh neutron-treated patients died of intercurrent disease or metastasis after becoming locally well. The corresponding figures for the Hammersmith trial are three out of 13 in the photon series and 18 out of 34 neutron-treated patients. The time-specific risk of

TABLE X

RADIATION-RELATED MORBIDITY

	Edinburgh		Hammersmith	
	Neutrons	Photons	Neutrons	Photons
Skin/subcutaneous tissue				
No. of patients assessed	54	50	46	30
Severe	7	2	13	1
Fatal	0	0	1	0
Larynx/mucous membrane				
No. of patients assessed	50	47	38	9
Severe	11	15	7	3
Fatal	3	0	7	0
Salivary glands				
No. of patients assessed	49	42	34	19
Severe	8	5	10	2
Fatal	0	0	0	0

There were two other deaths due to radiation myelopathy following neutron therapy.

TABLE XII

Model	Factors	Model comparison
(a) Death: treatment by risk score interaction		
1	Main effects: neutron, Edinburgh trial, risk score	1 vs 2 ($\chi^2_1 = 5.64$)
2	Main effects plus treatment × risk score interaction	
3	Main effects plus treatment × trial interaction	1 vs 3 ($\chi^2_1 = 7.34$)
4	Main effects plus treatment × risk score interaction	1 vs 4 ($\chi^2_2 = 10.88$)
	treatment × trial interaction	3 vs 4 ($\chi^2_1 = 3.54$)
(b) Death: treatment by disease severity interaction (coded 1, 2, 3)		
1	Main effects: neutron, Edinburgh trial, site, age, disease severity	1 vs 2 ($\chi^2_1 = 2.42$)
2	Main effects plus treatment × severity interaction	
3	Main effects plus treatment × trial interaction	1 vs 3 ($\chi^2_1 = 6.94$)
4	Main effects plus treatment × severity interaction	1 vs 4 $\chi^2_2 = 7.74$
	treatment × trial interaction	3 vs 4 $\chi^2_1 = 0\ 80$

dying from intercurrent disease or metastasis was significantly higher for patients treated by neutrons (Table VIII, Column 4, Model A).

Radiation-related morbidity

The assessment of late radiation morbidity was made retrospectively in both trials according to an agreed scale based on the RTOG/EORTC system (Table IX); formal assessment of late radiation morbidity was made at routine follow-up in the Edinburgh trial, but scoring was not defined in the Hammersmith protocol. For skin and subcutaneous tissue and for larynx and mucous membrane the greater of the scores at the two specified sites is used in Tables X and XI.

There was a significantly higher incidence of severe reactions (Grades 3, 4, 5) of the skin and subcutaneous tissues in assessed patients treated by neutrons (21%)

TABLE XI

RADIATION-RELATED MORBIDITY BY MAXIMUM NORMAL TISSUE DOSE

	Photon TDF*				Standardised neutron dose*		
	< 98	98–108	109–115	116+	14.0–15.49	15.5–16.49	16.5†
Skin/subcutaneous tissue							
No of patients assessed	4	30 (23)†	24 (22)	9 (4)	21 (17)	39 (32)	39 (5)
Severe		1 (1)		2 (1)	3 (1)	6 (3)	11 (3)
Fatal							1
Larynx/mucous membrane							
No. of patients assessed	1	23 (22)	21 (20)	7 (4)	17 (14)	36 (31)	35 (5)
Severe		7 (7)	7 (6)	3 (2)	5 (3)	7 (6)	6 (2)
Fatal						3 (2)	7 (1)
Salivary glands							
No of patients assessed	2	25 (20)	19 (17)	6 (4)	20 (16)	33 (28)	24 (5)
Severe		1 (1)	3 (3)	1 (1)	4 (2)	7 (6)	7 (0)
Fatal							
Total No. of patients	6	34 (26)	30 (26)	12 (7)	23 (18)	42 (34)	42 (6)

*See text for explanations of method of calculation.

†Total numbers in each subgroup are given with numbers of Edinburgh patients in parentheses.

than in those treated by photons (4%). Twenty-two per cent of assessed neutron-treated patients had severe late radiation morbidity of the salivary glands compared with 11% of photon-treated patients, but the difference is not statistically significant.

For larynx and mucous membrane, the overall incidence of severe reactions (Grades 3, 4, 5) was similar in the two treatment groups. However, in the two photon series there were no fatal complications amongst the 18 patients with severe reactions, whereas 10 of the 28 assessed neutron patients with severe reactions died of radiation-related morbidity, a clinically as well as statistically significant difference ($\chi_1^2 = 8.26$, $p < 0.02$, Table X), which contributed to the results on treatment failure presented above. Seven of the 10 who died were in the Hammersmith trial.

In addition, three neutron-treated patients had severe (Grades 4, 5, 5) late radiation morbidity of the spinal cord. The two patients who died were treated in the Hammersmith trial. Two Edinburgh photon-treated patients had radionecrosis of the mandible.

Table XI, which relates treatment morbidity to standardised maximum normal tissue dose, shows how highly confounded are centre and dose. Only six of 42 assessed neutron patients whose standardised maximum normal tissue dose exceeded 16.5 Gy were in the Edinburgh trial. It is, therefore, difficult to distinguish an effect of dose on late radiation morbidity from an effect associated with the centre at which treatment was given.

No clear-cut inference about dose–response can be made. At most, we can say that there is some indication of a neutron dose–response relationship, both in skin and subcutaneous tissue (incidence) and in larynx and mucous membrane (degree). In larynx and mucous membrane 0 out of 5, three out of 10 (30%) and seven out of 13 (54%) of severe reactions proved fatal in the low-, middle- and high-dose groups, respectively (Table XI). The 10 patients who died directly from these radiation-related complications received a neutron absorbed dose of 15.5 Gy or more. With neutron doses less than 15.5 Gy the incidence of severe morbidity in larynx and mucous membrane was similar but there was no treatment-related mortality.

Among the 40 patients who were assessed as being free of local disease at death, 11 (28%) died of treatment-related complications. No treatment-related mortality was associated with photon therapy.

TABLE XIII

Hammersmith photon-treated patients who received TDF less than 93 or TDF unknown

Age (years)	Site of tumour	Stage	field size (cm)	Dose (cGy)	TDF	Comments
86	Oral cavity	T_3N_3	10 × 8	5500/30/42	85	
63	Oral cavity	T_3N_3	8 × 10	600/33/51	91	
53	Oral cavity	T_2N_0	5 × 7	4500/17/27	85	5-year follow-up
40	Oral cavity	T_3N_0	6 × 8.5	6700/43/84	90	Emergency tracheostomy
73	Oral cavity	T_4N_3	7 × 12	3800/19/26	62	Died during treatment
66	Oral cavity	T_3N_3	7 × 11	?/32/53	—	
68	Oral cavity	T_3N_1	6 × 6	4900/12/25	109*	
83	Oropharynx	T_3N_3	10 × 14	5200/26/40	83	
70	Oropharynx	T_2N_3	16 × 12	4500/20/27	78	
76	Oropharynx	T_3N_3	14 × 8	?/31/44	—	
47	Oropharynx	T_4N_0	10 × 8.5	3010/11/14	59	3-year follow-up; alcoholic
82	Oval cavity	T_3N_2	10 × 10	5000/20/43	86	
70	Larynx and hypopharynx	T_4N_3	11 × 6	5000/20/29	91	
58	Oral cavity	T_3N_3	10 × 13	5000/25/34	82	
62	Larynx and hypopharynx	T_4N_3	17.5 × 18.5	4420/12/30	90	
66	Larynx	T_3N_0	?	600/3/3	—	Died during treatment
64	Larynx	T_3N_3	16 × 10	4420/22/31	73	
72	Larynx	T_3N_3	11 × 13	4000/12/27	79	
69	Larynx	T_3N_0	8 × 10	4500/12/27	79	
60	Larynx	T_3N_2	12 × 8	5500/25/43	91	5-year follow-up

*This TDF relates to a patient whose TDF was unknown at the time of analysis.

TABLE XIV

Summary of analysis (TDF and 40 day restriction: 190 patients)

	(1) Overall mortality (135 deaths)	(2) Time to locally well (130 locally well)
Explanatory variables		
Oral cavity		
Oropharynx	√√	
Larynx	√√	√√√
Age 65 or less		×
Severity 2	× × ×	× × ×
Severity 3	× × ×	×
Regression coefficients (|*t*| value): treatment and trial effects		
(A) Common neutron effect	−0.13 (0.66)	0.17 (0.93)
Edinburgh trial	0.07 (0.36)	0.39 (1.87)
(B) Edinburgh neutron effect	0.44 (1.77)	0.13 (0.61)
Hammersmith neutron effect	−0.30 (1.07)	0.26 (0.76)
Edinburgh trial	−0.37 (1.28)	0.47 (1.40)
Model preference	A	A
χ_1^2	2.20	0.10

R. restriction to 40 days survival and TDF > 93.
× or √, $0.10 > p > 0.05$.
× × or √√, $0.05 > p > 0.01$
× × × or √√√, $0.01 > p$.

Restricted series

It has been confirmed in this review that the neutron doses used at Hammersmith were, on average, 5% higher and the photon doses, on average, 10% lower than those delivered in Edinburgh. It is possible that the differences in results of the two series may be a consequence of differences in dose. Some of the patients in the photon group treated at Hammersmith received particularly low doses. In order to examine the influence of photon dose, a restricted analysis was made from which patients whose TDF was unknown or less than 93 were excluded, together with patients (neutrons and photons in both series) who died during or soon after treatment (within 40 days). A TDF of 93 corresponds to a dose of 50 Gy in 20 fractions in 4 weeks. The median dose of the excluded group is 85 (corresponding to 47.5 Gy in 20 fractions in 4 weeks); particulars of these photon patients who received TDF of less than 93 are set out in Table XIII.

Table XIV reports the proportional hazards analysis for the restricted series. In terms of the time to complete regression of local disease, the effect of neutrons and photons is similar in both centres (Column 2). In respect of overall mortality (Column 1) the previous highly significant "trial by treatment" interaction is much diminished and the results do not differ significantly between neutron and photon therapy. However, the Edinburgh and Hammersmith neutron effects continued in opposite directions. The fact that the difference between the two trials is no longer statistically significant is due, at least in part, to the reduced number of patients.

The estimated treatment effects in the restricted series carry no randomisation guarantee but any imbalance in known prognostic factors in the Hammersmith photon group is taken into account by the proportional hazards analysis. No other analysis was performed in the restricted series because only one patient who was excluded became locally well.

Discussion

The clinical trials of fast-neutron therapy for head and neck cancers conducted at the MRC Cyclotron Units at Hammersmith Hospital, London and the Western General Hospital, Edinburgh have been thought to have produced conflicting results. This study was undertaken as an attempt to identify and to understand these apparent differences. The two trials studied in this review differed in several aspects (Table I). The most important differences were in the stage of disease (Table V), the prescribed photon and neutron doses and the years in which the trials were carried out. Three sites, in particular, in the Hammersmith trial (salivary gland, antrum and neck nodes) were not included in the Edinburgh trial and were excluded from the present analysis. This review is concerned only with the four sites common to both trials. The proportional hazards analysis adjusts for differences of site, age and disease severity.

The analysis estimates separate treatment effects for the two centres. This has demonstrated that the results of the two series are similar in three respects. Firstly, the two series are comparable in terms of treatment failure (defined as local recurrence or late radiation death) following local tumour control. The results are also consistent in associating an increased incidence of severe late radiation morbidity and of intercurrent deaths with neutron therapy.

In three other respects the results of the two series are different. At Edinburgh there was an advantage to the photon-treated patients in terms of overall mortality, whereas at Hammersmith the advantage was to those treated by neutrons. Secondly, the incidence of tumour regression for patients randomised to photons at Hammersmith was much lower than for neutrons, whereas in Edinburgh the two modalities gave similar results. Thirdly, the recurrence rate for patients treated by neutrons at Hammersmith was very low compared with that recorded for those treated by photons and this difference was not observed in the Edinburgh series.

One factor which could account in part for these differences is dose. The median *neutron* dose at Edinburgh was lower that that used at Hammersmith and, in contrast, the median *photon* dose was higher at Edinburgh than at Hammersmith. To examine the effect of photon dose on the results, a restricted series was analysed. The TDF restriction was set at an arbitrary level of less than 93 (50 Gy in 20 daily fractions). Analysis of the restricted series has partially resolved two of the differences which have been observed. The differences in overall mortality were no longer significant but remained in the same sense as before and no significant advantage to neutrons was seen in terms of "time to becoming locally well" in either series. Patients excluded by reason of low TDF may differ prognostically, however, from patients who received a higher TDF (regression analysis is not a substitute for randomisation).

The difference between recurrence rates in neutron-treated patients in the Edinburgh and Hammersmith trials is striking. It has been established previously that the Edinburgh and Hammersmith neutron beams are similar in their biological effectiveness. The physical dosimetry at the two centres has been compared and shown to be consistent. The dose per fraction at Hammersmith was 74% higher than in Edinburgh and 12 fractions instead of 20 were given, but variations in fraction size for neutron beams of this energy are usually considered experimentally to have little influence on biological effectiveness. The Hammersmith neutron doses were higher than those at Edinburgh and a lower recurrence rate would be expected for this reason alone. A dose–response relationship cannot be demonstrated with any certainty due to the small number of patients and the impossibility of separating the effect of dose and centre: almost half of the patients treated by neutrons at Hammersmith received a standardised central dose higher than the highest dose given in Edinburgh.

The incidence of radiation-related morbidity (skin and subcutaneous tissue) and mortality (larynx and mucous membrane) was significantly higher in neutron-treated patients than in those treated by photons. At both centres the neutron beams had poorer penetration and skin sparing in comparison with the linear accelerators and cobalt units used to treat the photon patients. This lack of skin sparing and the differential absorption of neutron dose in fat contributed to the increased radiation morbidity in skin and subcutaneous tissues. The larynx is now recognised as a sensitive tissue to neutron radiation, for which a reduced dosage is necessary (Catterall & Bewley, 1979; Duncan et al, 1984). The very large tumours treated in the Hammersmith trial often left substantial deficits when controlled by neutrons, which may have contributed to the morbidity. Two deaths were recorded at Hammersmith from radiation myelopathy but the safe dose of neutrons to the cord was not known at the time of the Hammersmith trial.

The higher neutron doses (maximum normal tissue dose greater than 15.5 Gy) which were used predominantly at Hammersmith were associated with a significant increase in radiation-related mortality. When late radiation death and recurrence of local disease are together regarded as treatment failure after local tumour regression, there is no clear treatment preference in either trial. The increased incidence of late, radiation-related deaths offset the observed reduction in the local recurrence rate in the Hammersmith trial. Patients who became locally well are, of course, treatment selected: the lower incidence of local tumour control in the Hammersmith photon series has already been noted. It was also noted that, amongst patients who became locally well, there was a significantly higher mortality due to intercurrent and metastatic disease in both neutron series when compared with the photon-treated series. No reason for this has been established but it may be due to morbidity associated with these poorly penetrating neutron beams.

In Edinburgh the local tumour control rates and the incidence of serious late radiation morbidity were similar for both neutron and photon therapy. In the Hammersmith series, where the neutron dose was, on average, 5% higher and the photon dose 10% lower than those in Edinburgh, both local tumour control and late radiation morbidity were significantly higher in the neutron-treated patients than in those treated by photons.

The limitations of this retrospective review must be respected. The number of patients analysed was small so that only large differences could reach statistical significance. It was often impossible to distinguish differences, real or fortuitous, in the effect of treatment, dose and centre.

The reduced recurrence rate and the improved life expectancy and tumour regression following neutron therapy at Hammersmith have not been confirmed by the Edinburgh trial. On the other hand, the two trials agree in finding greater morbidity and more intercurrent death in those whose tumours were controlled by neutrons. The high radiation-related mortality which was associated with higher neutron doses delivered tended to offset the low recurrence rate observed at Hammersmith.

The trials discussed in this paper were not contemporaneous and they differed in stage of disease as well as in the parameters of radiation dosage. Moreover, they compared the use of a poorly understood quality of radiation generated by inadequate equipment with standard megavoltage X radiation and telecobalt gamma radiation. General conclusions about the value of neutron therapy cannot be drawn from this limited review.

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Correction

Delayed reactions to urographic contrast media. By Philip N. Panto and Peter Davies. *British Journal of Radiology* (1986), *59,* 41–44.

Table V in this paper (p. 43), Patients suffering from symptoms of iodism, contained a misprint in the first column, "Cases (men)". The number of men receiving Conray 280 (first row) was 103 and not 1034 as was printed. We apologise for this error.

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A Phase I study of mixed (neutron and photon) irradiation using two fractions per day in the treatment of high-grade astrocytomas

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ABSTRACT

A Phase I study of the treatment of 50 patients with high-grade astrocytomas by mixed schedule (neutron and photon) irradiation given in 12 fractions over 4 weeks is reported. The neutron and photon fractions were separated each day by 2–3 h. A total neutron dose of 6.36 Gy (8% γ) and 20.40 Gy of photons was prescribed. Treatment was well tolerated and there was no clinical evidence of radiation-related morbidity in the brain. The median survival was 6.9 months, similar to that expected after photon irradiation alone. A multivariate analysis of prognostic variables is presented.

Treatment of high-grade astrocytomas in adults is palliative for almost all patients. Curative treatment by photon irradiation is thought to be compromised by tumour hypoxia and the ability of clonogenic tumour cells to repair sublethal radiation damage (Gerweck et al, 1977). Neutron irradiation has been used in the hope of circumventing such limitations, but has often resulted in unacceptable damage to normal brain (Catterall & Bewley, 1979). Previous investigations combining neutron and photon irradiation have used a mixed alternate day schedule (Laramore et al, 1978; Duncan et al, 1986) or a localised neutron boost following a course of photon irradiation (Battermann, 1980; Griffin et al, 1983; Breteau et al, 1984). No survival advantage, however, has been reported.

Another clinical strategy is to combine neutron and photon irradiation sequentially on the same day. It has been demonstrated that the relative biological effectiveness (RBE) of neutrons compared with X rays for division delay in Chinese hamster cells is independent of dose up to 3.2 Gy for fission neutrons (Ngo et al, 1977). The RBE values for induced delay are similar to the highest values observed for cell survival. Rasey et al (1977) has also reported higher RBE values for mitotic delay than for survival in EMT-6 cells *in vitro*. It is not yet known if the RBE for mitotic delay varies with neutron energy or the type of mammalian cell. In addition, Ngo et al (1981) have shown that high-linear energy transfer (LET) radiations and X rays produce sublethal damage independently which interact with each other, and so suggest that an additive or synergistic effect may result from a combination of high- and low-LET radiations. When high-LET radiation precedes the low-LET radiation, the survival curve of Chinese hamster cells, V79, shows a reduced shoulder (D_q) compared with the survival curve with X rays only. This effect is reduced as the interval between exposures is increased. The total effect of combining fractions of high- and low-LET radiations is complex, involving partial synchrony as a result of division delay, G2/M block and recovery from sublethal damage in different phases of the cell cycle.

It is not known whether there is a clinically beneficial differential effect on normal and malignant tissue. It was, therefore, considered to be worthwhile evaluating, in a Phase I study, the combination of d(15)+Be neutrons and megavoltage X rays, separated by 2–3 h, in the management of patients with high-grade astrocytomas. A basic constraint in the design of the study was the recognition that the tolerance dose of d(15)+Be neutrons alone fractionated over 4 weeks is 8.0 Gy and so the priming dose of high-LET radiation had to be relatively small. For this reason the number of fractions was limited to 12 in an overall time of 4 weeks.

PATIENT SELECTION AND METHODS

Fifty consecutive adult patients with histologically proven brain tumours were treated between January 1983 and August 1984. There were 38 males and 12 females. Patients with severe neurological deficits were eligible only if they were considered fit enough to complete radical treatment.

The neutron irradiation was obtained by accelerating 15 MeV deuterons onto a thick beryllium target. The beam was then collimated in an isocentric treatment head. The photon irradiation was given by a 4 MV linear accelerator. The whole brain was irradiated by a parallel opposed pair of fields (normally 11 cm × 16 cm). Patients were treated supine with the aid of a beam direction shell utilising front and back pointers to align the fields. A target absorbed dose of 0.53 Gy (8% γ rays) neutron irradiation followed after

2–3 h by 1.7 Gy photon irradiation was delivered each Monday, Wednesday and Friday. A total dose of 6.36 Gy neutrons (8% γ rays) and 20.4 Gy photons was delivered in 12 fractions over 4 weeks.

Dexamethasone, in doses of up to 16 mg per day, was used throughout radiation therapy and in the follow-up period as required. Patients were reviewed regularly following treatment and, in the event of clinical deterioration, further neurosurgical intervention was undertaken if indicated. No patient was re-treated with radiation or received cytotoxic chemotherapy. Post-mortem examinations were not routinely obtained. All histological material has been reviewed by a pathologist (A.G.).

Patient survival rates were calculated by the life-table method (Kaplan & Meier, 1958). Further analysis of survival data was performed using the proportional hazards regression model (Cox, 1972) to identify those factors which affected prognosis.

RESULTS

Table I shows the distribution of the histological characteristics of the tumours. Necrosis was strongly associated with vascular endothelial proliferation (VEP) ($p = 0.0004$). Two patients were identified as having pure oligodendrogliomas and five patients, mixed oligodendroglioma and astrocytoma. Table II shows the distribution of patients by age, MRC neurological status (MRC Working Party, 1983), length of history and presenting symptoms.

TABLE I

HISTOLOGICAL CHARACTERISTICS (NO OF PATIENTS)

	None	Slight	Moderate	Severe	Not known
Cellularity	—	7	17	21	5
Pleomorphism	2	15	14	14	5
Mitoses	11	23	8	1	7
VEP	10	11	13	9	7
Necrosis	16	10	7	12	5

TABLE II

PATIENT DETAILS

		Male	Female
Age (years)			
Mean		53.0	53.3
Range		19–67	27–71
No. of patients with			
neurological status:	MRC 1	6	4
	MRC 2	14	3
	MRC 3	10	3
	MRC 4	8	2
length of history.	< 6 months	28	7
	≥ 6 months	10	5
epilepsy as sole presenting symptom		12	5
dysphasia as a presenting symptom		12	3

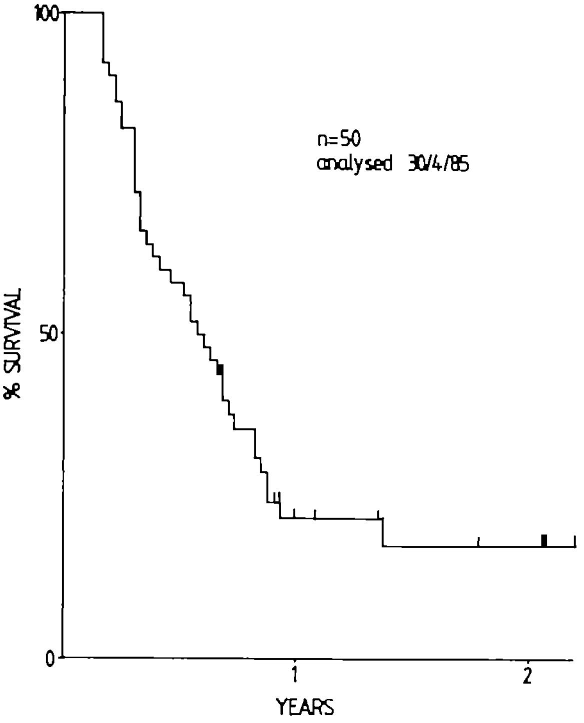

FIG. 1.
Length of survival of the patients studied.

Three patients failed to complete treatment because of deterioration of their physical condition.

Figure 1 shows the survival time of the patients. The minimum length of follow-up was 7 months. The median survival time was 6.9 months. Eleven patients remained alive by April 30, 1985, with a range of follow-up of 7–27 months.

The majority of deaths (36 out of 39) were attributed to progressive brain tumour. Only four post-mortem examinations were obtained. One patient was shown to have widespread metastatic astrocytoma and another demonstrated tumour deposits within the spinal subarachnoid space.

Seven patients developed evidence of thrombosis and in three patients pulmonary embolism resulted in the premature death of neurologically fit subjects. All were receiving dexamethasone at the time, but at different doses.

Analysis of prognostic factors

Age, sex, pathology, length of history, epilepsy and dysphasia as presenting symptoms and MRC neurological status before irradiation were considered as possible prognostic factors in the proportional hazards model. Epilepsy was removed from consideration first,

TABLE III

COVARIATES RETAINED IN THE MODEL

Covariate	Coefficient	p value
Length of history	−1.390	0.003
Sex	1.068	0.013
Neurological status	0.436	0.024
Age	0.034	0.090

since the presence of epilepsy as a presenting symptom was strongly associated with a long history. Dysphasia and pathology also proved to be of no prognostic value, though in the latter case this could have been due to the small numbers of patients with pure oligodendrogliomas and mixed tumours. Table III shows the covariates retained in the model. A prognostic index (I) was formed, given by the formula:

$$I = (0.034 \times \text{age}) + (1.068 \times \text{sex}) + (0.436 \times \text{neurological status}) - (1.390 \times \text{length of history})$$

where sex was coded as $1 = \text{male}$, $2 = \text{female}$, and length of history as $1 = < 6$ months, $2 = \geqslant 6$ months.

The minimum value (best prognosis) of I for the series of 50 patients was −0.194 and the maximum value (worst prognosis) was 4.836.

The patients were divided into two groups on the basis of their estimated prognostic index, depending on whether the value of I was greater than or less than 2.1 (where there was a natural break in the distribution of values of I).

The 16 patients with a good prognosis ($I < 2.1$) had a 2-year survival rate of 53.8%, while all but one patient in the poor-prognosis ($I > 2.1$) group of 34 patients were dead after 1 year (median 4 months). Only three patients with a short history were in the good-prognosis group, whereas only two patients with a long history were in the poor-prognosis group. The good-prognosis group contained only two patients with MRC neurological status 3 or 4, while there were 13 patients of neurological status 1 or 2 in the poor-prognosis group. All but one of the patients aged under 40 years were in the good-prognosis group, but only four of those were aged 55 years or more. The good-prognosis group contained 13 males but only three females.

A further analysis of prognostic factors was performed, including the five recorded histological characteristics of the tumour in place of pathology. However, since each of VEP, necrosis, pleomorphism and cellularity were associated with length of history (the most powerful prognostic variable included in the model), this did not add any information.

DISCUSSION

The natural history, response to treatment and prognostic indices of high-grade astrocytomas in adults have been reviewed recently (Byar, et al, 1983; Kelly et al, 1984). The overall prognosis is poor, although subgroups of younger patients with long histories, favourable histology and minimal neurological deficits do appear to have the prospect of longer than average survival. The influence of these factors on prognosis is confirmed in this study using a mixed schedule of neutron and photon irradiation. In addition, this study has shown that unfavourable histological characteristics (VEP and necrosis) are associated with each other and with a short history.

Our observation that female sex was associated with poor prognosis was unexpected. The male-to-female ratio in this study was 3.2 : 1, which was higher than we would normally expect, suggesting that this finding may be spurious.

Any survival benefit for the majority of patients which may result from more intensive radiation therapy must be weighed against the risk of late morbidity in patients with a better prognosis. In this study, no meaningful improvement in median survival has been observed compared with that reported after standard photon therapy. Apart from persistent epilation, no long-term radiation sequelae have been seen, but it is recognised that the maximum follow-up period is only 27 months.

Three patients died unexpectedly from pulmonary thromboembolism. Although a recognised terminal event in bed-bound patients with severe neurological deficits, occasional deaths occur in ambulant patients who are neurologically fit. Richardson (1978) suggested that dexamethasone may be an aetiological factor.

Thrice-weekly attendance was found to be convenient to patients and was well tolerated. Further studies of non-standard fractionation of neutrons or photons seem justified in attempting to improve the palliative management of patients with high-grade astrocytomas.

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Regional lung function impairment following post-operative radiotherapy for breast cancer using direct or tangential field techniques

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ABSTRACT

We have compared the effect of tangential and direct irradiation on regional lung function in 22 consecutive patients with breast cancer, who had been treated by post-operative irradiation 3 months prior to the examination. The tangential technique (total dose 32–36 Gy, < 5 Gy to the lung) was employed in eight of the patients, while the direct technique (total dose 40 Gy, 5–20 Gy to the lung) was used in the other 14. In the group that had been treated by the tangential technique, there was no impairment of the ventilation or perfusion of the irradiated lung compared with the contralateral lung. The radiographs of the thorax were all normal. In the group that had been treated by the direct technique, there was a reduction in both the ventilation and the perfusion in 12 of the patients ($p < 0.01$). The radiographs of the thorax were abnormal in only seven of these 12 patients. In both groups the regional leakiness of the lungs was evaluated as the pulmonary clearance of inhaled nebulised ^{99}Tc^{m}-DTPA. Due to differences in smoking habits between and within the groups, the results were not conclusive. It is concluded that the regional lung function was not significantly affected by the tangential technique, in contrast to a pronounced and harmful effect of the direct technique.

Radiation therapy became widely used for the treatment of malignant disease during the first two decades of this century. It was not until the third decade, however, when X rays of higher energy were used, that the earliest reports (Groover et al, 1922; Hines, 1922; Tyler & Blackman, 1922) of adverse effects on the lungs and the pleurae appeared. Emirgil and Heinemann (1961) characterised the effects of irradiation to the chest on pulmonary function in man. They described a decrease in lung volumes, an impairment of the diffusion capacity and an increase in the work of breathing.

To avoid excessive damage to the lungs following radiation therapy for cancer of the breast, tangential therapy has been used in many countries since 1926 (Holfelder, 1926). Chu et al (1955) demonstrated that a tangential technique reduces the incidence and severity of post-irradiation pneumonitis, as diagnosed by means of a radiograph. Recently, Sørensen et al (1984) found that severe impairment of regional ventilation and perfusion might be present in spite of a completely normal radiograph of the chest. The object of the present study was, therefore, to answer the question: does a tangential technique applied for irradiation of cancer of the breast affect the regional lung function?

We tried to answer the question by comparing the effect on regional ventilation, perfusion and leakiness of direct irradiation with that of tangential irradiation *ad modum* McWhirter (Kaae & Johansen, 1963). The regional ventilation and perfusion were studied by means of ventilation and perfusion scintigrams. The regional leakiness (Minty et al, 1981), indicative of the presence of fibrosis (Rinderknecht et al, 1980), was studied as the clearance of inhaled, nebulised ^{99}Tc^{m}-DTPA from the lungs.

Measurements of regional lung function allow separate evaluation of the function of the two lungs. The non-irradiated lung can serve as control. Thus, it is possible to study the effects at any point after the irradiation by direct comparison between the two lungs. In most patients radiation pneumonitis and fibrosis are most pronounced 3 months after the irradiation (Gross, 1977). We decided, therefore, to compare the effects of the two types of irradiation on the regional lung function 3 months after the completion of radiation therapy.

PATIENTS AND METHODS

Twenty-two consecutive women consented to participate. None of the patients had a history of previous lung disease, such as tuberculosis, pneumonia or pulmonary emboli. They had all been treated by simple mastectomy and post-operative radiation 3 months prior to the examinations. They were divided into two groups, according to the type of irradiation. Fourteen of the patients had been treated by direct irradiation from a linear accelerator (the "LA" group). Eight of the patients received tangential radiation *ad modum* McWhirter (Kaae & Johansen, 1963) (the "McW" group). In Table I, the anthropometric data of

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TABLE I

Characteristics of the patients (means ± standard errors)

Type of irradiation	No. of patients	Age (years)	Weight (kg)	Height (cm)	No. of non-smokers	Smokers		Irradiation changes present on chest radiograph
						No.	Tobacco per day (g)	
Linear accelerator (LA)	14	51.6±2.9	63.4±1.7	163.6±1.7	3	11	21.1±1.6	7
McWhirter (McW)	8	65.9±2.1	82.5±2.9	164.5±3.4	4	4	8.2±1.2	0

the two groups are given, together with their smoking habits.

Irradiation techniques

The predominantly direct irradiation was delivered by a linear accelerator at a FSD of 100 cm. Three fields were used: supraclavicular anterior, chest-wall medial and tangential chest-wall lateral. Twenty-two doses of 1.85 Gy were delivered giving a total dose of 40 Gy to the chest wall and 5–20 Gy to the lung.

The predominantly tangential irradiation was given by a 300 kV unit. The technique was designed to irradiate adequately the chest wall, the lymphatic channels and the regional lymph nodes *en bloc*. To avoid irradiation of the lung as much as possible, four fields were used: medial tangential, lateral tangential and anterior and supraclavicular posterior. Fifteen doses of 2.1–2.5 Gy were delivered, giving a total dose of 32–37 Gy to the chest wall and the skin and < 5 Gy to the lung.

Lung volumes, flow variables and diffusion capacity

Spirometry was performed on computerised Jaeger equipment. Inspiratory vital capacity (VC) was measured three times and the best result used (Berglund et al, 1963). Total lung capacity (TLC) and residual volume (RV) were measured by means of a single-breath helium dilution method. The forced expiratory volume in 1 s (FEV_1), peak expiratory flow-rate (PEF) and forced expiratory flow-rate at 50% of the vital capacity (MEF_{50}) were calculated from the best of three flow–volume curves. The diffusion capacity was measured as the transfer factor (TL_{CO}) by a single-breath method. The different lung function variables were expressed as per cent predicted (Berglund et al, 1963; Hedenstierna et al, 1981; Cotes & Hall, 1970).

Regional lung function

Radionuclides. Sodium pertechnetate ($^{99}\text{Tc}^{m}\text{O}_4^-$) was eluted in isotonic saline from a $^{99}\text{Mo}/^{99}\text{Tc}^{m}$ generator (IRE). The $^{99}\text{Tc}^{m}$ was chelated to diethylenetriamine-penta-acetate (DTPA) (New England Nuclear), introducing 20 mCi of $^{99}\text{Tc}^{m}\text{O}_4^-$ into a kit containing 3.3 mg of DTPA in a maximum volume of 5 ml isotonic saline. The $^{99}\text{Tc}^{m}$-DTPA (molecular weight 492 daltons) was made 1 h before use. The binding of $^{99}\text{Tc}^{m}$ to DTPA was found to be 97% complete by chromatography, where the separation of $^{99}\text{Tc}^{m}$-DTPA and $^{99}\text{Tc}^{m}\text{O}_4^-$ was achieved with acetone on silica gel strips.

Human albumin microspheres were made by introducing 5 ml $^{99}\text{Tc}^{m}\text{O}_4^-$ into a kit containing the microspheres (TCK-5; CIS), 99% of which had a diameter between 23 μm and 45 μm when suspended. Less than 5% $^{99}\text{Tc}^{m}$ was free after the labelling procedure. The suspended microspheres were shaken vigorously immediately before withdrawing the dose for injection.

Aerosol generation and administration. The aerosol was generated in an ultrasound nebuliser (de Vilbis nebuliser, 35B) containing the 20 mCi $^{99}\text{Tc}^{m}$-DTPA. The aerosol was inhaled from the nebuliser and, on its way to the mouth, it passed a 10 l container and a 1 m-long hose to permit settling of larger droplets (Rinderknecht et al, 1980). A T-valve at the mouth ensured that the expirated air could be collected in a trap. The patient inhaled the aerosol at slightly deeper inspirations than tidal volume. Each inspiration was slow and was followed by a 3 s pause (breath held) before each expiration. The inhalation was made with the patient in the sitting position. The aerosol was administered for a maximum of 3 min, yielding a count-rate of 120 000 counts/min over the entire lung field. The background count-rate was 500–1000 counts/min.

Data acquisition. Immediately after the inhalation of the aerosol, the patient was seated, with her back against an Anger-type scintillation gamma camera (LFOV, Searle Radiographic Inc.) with a standard field-of-view size crystal and a parallel 140 keV collimator. Dynamic acquisition of the detected lung-field radioactivity was made for 10 min on a computer (MED II, Nuclear Data). The acquisition was framed at 20 s intervals. After 2 h, the patient was reseated in front of the gamma camera and 5 min of acquisition was made in "list mode" to enable a background correction to be performed for the subsequent perfusion scintigraphy. This was immediately followed by an intravenous injection of 4 mCi TCK-5 and another 5 min of acquisition was made in list mode. During the acquisition, ventilation and perfusion scintigrams were made on Polaroid films.

Data processing. The acquired data were processed to display initial distribution of the activity of $^{99}\text{Tc}^{m}$-DTPA. Regions of interest were created and the

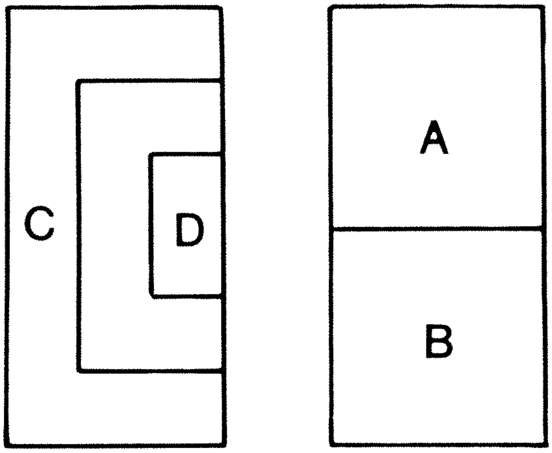

FIG. 1.

Regions of interest. The midpoint of the height of the healthy lung was used to divide the lungs into an upper (A) and a lower (B) quadrant. The height and the width of the healthy lung were intersected into thirds, and the peripheral (C) and central (D) parts of the lungs were defined as shown.

percentage ventilation ($\dot{V}$) of the upper and the lower quadrant of each lung was calculated by subtracting the regional background count-rate from the initial regional count-rate registered in the upper and lower quadrant of each lung (Fig. 1A, B) after the inhalation of the ^{99}Tc^{m}-DTPA. The regional difference between the radioactivity registered during the 5 min before and after the injection of TCK-5 was used to calculate the percentage distribution of the perfusion ($\dot{Q}$) of the lungs for the same regions of interest. A $\dot{V}/\dot{Q}$ ratio was determined for each of the regions. Pulmonary clearance of ^{99}Tc^{m}-DTPA, (P–Cl) was calculated by applying a monoexponential fit to the time–activity curve. The size of the P–Cl was characterised by the negative slope of the time–activity curve (Rinderknecht et al, 1980). Correction was made for physical decay of the ^{99}Tc^{m}. P–Cl was calculated for the upper and lower quadrant of each lung (Fig. 1A, B) and for central and peripheral parts of the lungs (Fig. 1C, D).

Radiographs. Plain chest radiographs were obtained in two projections.

Statistical analysis. Comparison between the regional lung function of the irradiated and the contralateral lung within the same group was performed by means of a t-test for paired samples. Comparison between the results of the two groups was made by a t-test for unpaired samples.

RESULTS

Spirometric evaluation of the global lung function

The results of the spirometric examination are given in Table II. There was an impairment of the lung function of the LA group indicative of the presence of a mixed pattern of restrictive and obstructive function disease. The restrictive component of this pattern was composed of a reduction of VC ($p < 0.01$) and of TL_{CO} ($p < 0.01$) (Table II). The obstructive component was an increase of RV/TLC ($p < 0.05$) and a reduction of MEF_{50} ($p < 0.01$). There was also a reduction of FEV_1 and PEF ($p < 0.05$) but this was no more pronounced than the reduction of VC and it could be explained by this reduction.

In the McW group, the lung volumes and flow variables were all within normal range. There was a reduction of TL_{CO} ($p < 0.05$), but this was only moderate and differed significantly ($p < 0.01$) from the severe reduction of TL_{CO} in the LA group.

Regional lung function

The examination of the regional lung function revealed a marked difference between the effect of the two types of irradiation on the lungs. The distributions of the ventilation and the perfusion in one patient from the LA group and one patient from the McW group are given in Fig. 2 as an example.

Regional ventilation. In the LA group, the ventilation of the irradiated lung (I) was significantly ($p < 0.01$) reduced compared with the contralateral lung (C) (Table III). The difference was most pronounced ($p < 0.01$) for the upper quadrant, but was even significant ($p < 0.05$) for the lower quadrant of the lungs. In the McW group, the ventilation of the irradiated lung was insignificantly reduced compared with the contralateral lung.

There was no significant difference between the percentage ventilation of the irradiated lungs of the two groups. On the Polaroid ventilation scintigrams, however, 12 of the 14 patients in the LA group had a defect in the irradiated area; this was not seen in any of the patients in the McW group ($p < 0.02$).

Regional perfusion. In the LA group there was a significant reduction in the perfusion of the irradiated

TABLE II

LUNG FUNCTION (% OF PREDICTED MEAN VALUES ± STANDARD ERRORS) OF THE TWO GROUPS 3 MONTHS AFTER IRRADIATION

	TLC	VC	RV/TLC	FEV_1	PEF	MEF_{50}	TL_{CO}
LA	95.74±2.94	85.48±3.96	125.39±6.59	82.69±4.14	87.22±4.56	68.33± 6.60	50.53±2.47
McW	115.93±3.31	106.16±7.31	97.30±4.85	106.24±7.72	96.03±2.89	113.03±12.21	86.03±3.24
LA – McW	$p < 0.001$	$p < 0.05$	$p < 0.01$	$p < 0.05$	NS	$p < 0.005$	$p < 0.001$

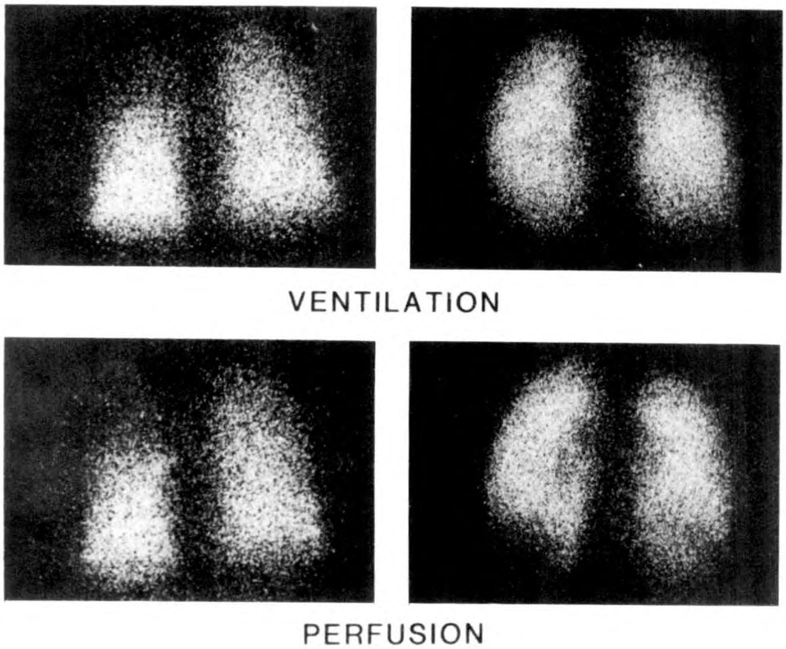

FIG. 2.

An example of the distribution of the ventilation and the perfusion in two patients. Both patients had been irradiated for cancer of the breast 3 months prior to the examination. Left: direct irradiation from a linear accelerator. Right: irradiation by a tangential technique *ad modum* McWhirter.

side compared with the contralateral side. The reduction of the perfusion of the upper part of the irradiated lung was more pronounced ($p < 0.05$) than of the lower. In the McW group, the difference between the irradiated and contralateral lung was not significant.

In contrast to the ventilation, there was a significant difference in the percentage perfusion of the irradiated lung between the two groups. There was a defect on the Polaroid perfusion scintigrams in the area of ventilation in the 12 patients of the LA group in whom a ventilation defect was observed, while none of the patients in the McW group showed any perfusion defect ($p < 0.02$).

V/Q relationship

Due to the fact that the perfusion of the irradiated lung of the LA group was slightly more reduced than the ventilation, the V/Q ratios of the irradiated lungs were slightly higher than of the contralateral lung. However, this difference was not significant. There were no trends of V/Q mismatch in the McW group. The V/Q ratio of the upper half of the irradiated side of the LA group was significantly higher than that of the McW group ($p < 0.01$). This difference was also reflected in the results for the whole lungs ($p < 0.05$).

Regional clearance of ^{99}Tc^{m}*-DTPA*

The pattern of the regional clearance of ^{99}Tc^{m}-DTPA from the lungs of the two groups was not as uniform as the pattern of ventilation and perfusion. In the LA group there was no significant difference between the P–Cl of the irradiated and contralateral lung (Table IV). This lack of difference did not mask different tendencies within the lungs since there were no significant differences between the irradiated and contralateral lung for any of the regions of interest. In the McW group, however, the clearance of the lower half was significantly faster on the irradiated side than on the contralateral side. This difference was paralleled by a similar trend of the upper half and of the periphery.

There was a marked difference in the pulmonary clearance of the upper half of the lungs between the two groups ($p < 0.01$), predominantly for the peripheral parts of the lungs. There was also a significant difference between the two groups in the P–Cl of both lungs ($p < 0.05$) and each lung ($p < 0.05$), but this is probably only a reflection of the differences between the upper quadrants and the periphery.

DISCUSSION

The results of this study show that the regional function of the lungs is only slightly or not at all affected by the dose of < 5 Gy which is delivered to the lung by tangential radiation therapy *ad modum* McWhirter for cancer of the breast. If, on the other hand, the dose to the lungs is 5–20 Gy, as was the case for the LA group in this study, there is a marked impairment of the regional function.

The normal pattern of ventilation and perfusion of the McW group, which was observed 3 months after the irradiation, is in agreement with the results of the radiographic examination of the chest. In the LA group, however, there was a discrepancy between the changes observed in the radiograph of the chest and

TABLE III

COMPARISON OF THE IRRADIATED LUNG (I) AND THE CONTRALATERAL LUNG (C) WITH REGARD TO VENTILATION (V), PERFUSION (Q) AND V/Q RATIO (MEANS ± STANDARD ERRORS)

	Upper quadrant			Lower quadrant			Whole lung		
	I	C	(I−C)	I	C	(I−C)	I	C	(I−C)
Ventilation % (V)									
LA	15.7±1.1	22.2±1.2	− 6.5±1.1*	26.9±2.0	35.2±1.1	− 8.3±2.4†	42.6±1.2	57.4±1.2	−14.8±0.5*
McW	20.5±1.3	22.9±1.2	− 2.4±1.0	26.5±1.4	30.1±1.9	− 3.6±2.4	47.0±1 7	53.0±1.7	− 6.0±3.4
LA−McW	NS	NS		NS	NS		NS	NS	
Perfusion % (Q)									
LA	13.4±1.2	29.9±4.1	−16.5 ±3.7†	19.3±3.5	37.4±2.9	−18.1±3.3†	43.3±2.8	56.7±3.9	−13.4±5.6‡
McW	25.6±1.5	26 4±1.7	− 0.74±2.2	22.5±1.8	25.4±1.4	− 2.9±2.3	48.1±2.1	51.8±2.1	− 3.7±4.1
LA−McW	$p < 0.001$	NS		NS	$p < 0.01$		$p < 0.05$	NS	
V/Q ratio									
LA	1.17±0.1	0.74±0.1	0.43±0.2	0.88±0.3	0.94±0.1	− 0.06±0.2	0.98±0.1	0.70±0.04	− 0.28±0.1
McW	0.8 ±0.1	1.0 ±0.1	− 0.2 ±0.1	1.1 ±0.1	1.1 ±0.1	0.0 ±0.1	0.9 ±0.1	1.0 ±0.1	− 0.1 ±0.2
LA-McW	$p < 0.001$	NS		NS	NS		$p < 0.05$	NS	

*$p < 0.001$
†$p < 0.05$
‡$p < 0.01$

TABLE IV

PULMONARY CLEARANCE (KCOUNTS/MIN) OF $^{99}Tc^{m}$-DTPA FROM THE LUNGS OF THE TWO GROUPS OF PATIENTS 3 MONTHS AFTER IRRADIATION (MEANS ± STANDARD ERRORS)

		LA	McW	LA−McW
Both lungs		-0.036 ± 0.025	-0.013 ± 0.0084	$p < 0.05$
Whole lung	I	-0.033 ± 0.0064	-0.015 ± 0.0029	$p < 0.05$
	C	-0.031 ± 0.0076	-0.011 ± 0.0026	$p < 0.05$
	I−C	NS	NS	
Upper quadrant	I	-0.040 ± 0.0084	-0.00080 ± 0.0054	$p < 0.001$
	C	-0.044 ± 0.010	-0.00069 ± 0.0045	$p < 0.01$
	I−C	NS	NS	
Lower quadrant	I	-0.030 ± 0.0060	-0.028 ± 0.0033	NS
	C	-0.028 ± 0.0066	-0.020 ± 0.0028	NS
	I−C	NS	$p < 0.1$	
Peripheral parts	I	-0.030 ± 0.0093	$-0.024 \pm 0\ 0037$	NS
	C	-0.035 ± 0.0066	-0.012 ± 0.0045	$p < 0.001$
	I−C	NS	NS	
Central parts	I	-0.033 ± 0.0094	-0.011 ± 0.0041	NS
	C	-0.026 ± 0.0075	-0.0099 ± 0.0029	NS
	I−C	NS	NS	

I = irradiated lung; C = contralateral lung.

the impairment of ventilation and perfusion of the irradiated parts of the lungs. In five of the 14 patients there was a reduction of the ventilation and the perfusion which was not anticipated from the radiographs. These results, therefore, support the observation by Sørensen et al (1984), that many patients who are in complete radiographic remission after chemotherapy for small-cell anaplastic lung carcinoma may have significant defects in V and Q. Thus, it does not seem to be sufficient to diagnose and monitor iatrogenically induced or spontaneously occurring changes by means of a plain radiograph only.

The only indication of a slight effect on the regional lung function in the patients of the McW group was provided by the results of the measurements of the pulmonary clearance of $^{99}Tc^{m}$-DTPA. There was an increased clearance in the lower part compared with the contralateral part and a similar trend in the upper half and the peripheral part of the whole lung, but this trend was not limited to the area of irradiation. Sawtantra et al (1979) found that in patients with systemic sclerosis there was an increase in pulmonary clearance of $^{99}Tc^{m}$-DTPA, which was most pronounced for the dependent parts of the lungs. Radiation pneumonitis is not necessarily restricted to the field of irradiation (Ross, 1956; Smith, 1964; Rubin & Casarett, 1968; Bennett et al, 1969; Cohen et al, 1974) and the observed increase in pulmonary clearance of $^{99}Tc^{m}$-DTPA may, therefore, reflect a diffuse alteration of the integrity of the epithelial lining of the irradiated lung compared with the contralateral lung.

In the LA group, however, there was no significant difference between the $^{99}Tc^{m}$-DTPA P–Cl of the two lungs. It cannot be excluded that this lack of difference reflects an even more comprehensive and diffuse deterioration of the epithelial lining of the lungs, but the smoking habits of the LA group are a more obvious reason.

Jones et al (1980) demonstrated that the lungs of smokers are more permeable to $^{99}Tc^{m}$-DTPA than the lungs of non-smokers, and Mason et al (1983) found that the increased permeability was predominantly located to the apical parts of the lungs. The pattern of difference in $^{99}Tc^{m}$-DTPA P–Cl between the LA group and the McW group in this study was very much like the expected difference between a group of smokers and one of non-smokers. This is not surprising if the composition of the two groups, with regard to smoking habits, is considered. Eleven of the 14 consecutive patients in the LA group were heavy smokers (Table I), while only one of the eight patients in the McW group was a heavy smoker and three of them smoked less than five cigarettes per day. Therefore, the increase in $^{99}Tc^{m}$-DTPA clearance of the LA group compared with the McW group is far more likely to be a reflection of the differences in smoking habits of the two groups than a reflection of the differences in radiation technique.

The differences between the regional lung function of the two groups was paralleled by a similar difference in lung volumes and diffusion capacity. In the LA group, the reduction of V and Q was accompanied by a reduction of VC and TL_{CO}, while in the McW group, the only indication of a radiation injury was slightly lower values of TL_{CO} than should be expected if the group had not been irradiated.

In conclusion, the serious effects on regional lung function following irradiation for cancer of the breast by the predominantly direct technique are in marked contrast to the changes of regional lung function following irradiation by a tangential technique *ad modum* McWhirter. The latter are too small to be of any clinical importance. Irradiation by means of a tangential technique, therefore, seems to be the radiation therapy of choice if the clinical situation makes it desirable that as much of the lung function as possible should be preserved.

ACKNOWLEDGMENT

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Book reviews

Linear Accelerators for Radiation Therapy. Medical Physics Handbooks 17. By D. Greene, pp. xii + 194, 1985 (Adam Hilger, Bristol), £19.50/$33.00.
ISBN 0-85274-557-5

This seventeenth Medical Physics Handbook from Adam Hilger is, I believe, long overdue but well worth waiting for. David Greene has produced a very readable account of the workings and applications of linear accelerators for radiotherapy. It is intended as a book for physicists—and should be compulsory reading for all radiotherapy physicists—but its relaxed, non-mathematical style will also appeal to trainee radiographers and radiotherapists. The text takes the reader through every aspect of the accelerator in the radiotherapy department from the basic waveguide theory to its operation and maintenance, concluding with chapters on the design of treatment rooms and the simulator. The extensive list of references enables the reader to deepen his study of areas of particular interest.

The first three chapters concentrate on the acceleration of the electrons down the waveguide. With simplified diagrams and a straightforward description, the author outlines the similarities and differences between the standing wave and travelling wave systems together with each major component in the acceleration process. The next section, about half of the book, deals with the treatment head and all the aspects relating to the application of the beam to the patient. This is followed by two, more physics-orientated chapters on specification, performance and maintenance, including both short-term and long-term quality assurance aspects.

The author's long experience in this field has enabled him to produce a comprehensive account without unnecessary duplication of other standard texts.

C. K. BOMFORD

Primary Management of Breast Cancer. Alternatives to Mastectomy. Ed. by J. S. Tobias and M. J. Peckham, pp. vi + 220, 1985 (Edward Arnold, London), £32.50.
ISBN 0-7131-4465-3

The primary management of breast cancer has changed in a number of ways during the last 10–20 years and is still changing. Dr Jeffrey Tobias and Professor Michael Peckham have put together an excellent book describing the changes taking place and the experiences which have led up to them. A team of expert clinicians from Great Britain, the United States and Europe have written well informed and well researched chapters covering all aspects of the new approaches to management. Anyone who is uncertain of recent developments will find all they need in this book. It should get them completely up to date.

Surgical techniques, including methods of reconstruction, and radiotherapy techniques are described in detail and consideration is given to the results of clinical trials and to the role of adjuvant therapy. The psychological effects on the patients of the different treatments are considered and there is an interesting chapter from a non-medical expert who describes the point of view of the public. The book is dedicated to Sir Geoffrey Keynes who was one of the first to question the necessity for mastectomy and who advocated radical radiotherapy.

I can recommend this book highly to all those interested in the endless problems of the management of primary breast cancer. The chapters are well summarised in discussion in concluding paragraphs. £32.50 will purchase a mine of valuable information, presented in a clear, accurate and easily assimilated form.

DIANA BRINKLEY

1986, *The British Journal of Radiology*, *59*, 453–456 MAY 1986

A comparison of the costs of vascular surgery and balloon dilatation in lower limb ischaemic disease

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ABSTRACT

The length of stay in hospital was recorded for 24 patients admitted for investigation and treatment of vascular disease of the lower limb and a detailed analysis of the costs incurred was made for 10 patients. It was found that the mean cost of angiography and surgery was £1577 and of angiography and dilatation, £301. The major factor in the cost difference was the shorter hospital stay for dilatation, with lesser factors being the use of fewer staff and the avoidance of general anaesthesia.

Balloon catheters for the percutaneous dilatation of arterial stenoses and occlusions were introduced some 10 years ago (Gruntzig & Hopff, 1974) and, after initial use in Europe, became accepted in the United States and then the United Kingdom (Cumberland, 1982). Most new techniques cost more money than the old, but it is claimed in the United States that balloon dilatation is unusual in that it can save unnecessary morbidity, mortality *and cost* (Doubilet & Abrams, 1984). In the UK the costs of the technique have not been estimated, although the need for this to be done has been recognised (Anonymous, 1984). Analysis of the costs incurred in particular treatments may give new information leading to changes in the way the treatment is carried out and can result in the better use of resources (Drummond & Mooney, 1982). The introduction of any new method of treatment involving a department different from that using the older method has implications both for the hospital and for budget holders when management budgets are introduced (Davies & Prowle, 1984). It will also affect any costing system based on the "Diagnostic Related Group" concept (Scott & Sherwood, 1984).

Balloon angioplasty is now an accepted technique in this hospital and has an established place in the treatment of our patients with peripheral vascular disease (Campbell et al, 1983). We, therefore, decided to calculate the costs of both the new technique and the established techniques of aorto-femoral and femoro-popliteal bypass surgery as the first step in assessing the effects of introducing the new technique.

PATIENTS AND METHODS

The length of stay was measured for 24 patients admitted to the Bristol Royal Infirmary for investigation and treatment of vascular disease of the lower limb. A detailed analysis was made of costs incurred for 10 patients during admission, based on the method developed in Southampton (Mollo, 1982). Costs were calculated by using specially designed and previously tested forms, some of which were completed by staff and some by a trained observer (R.M.D.). After the patient's discharge from hospital, the costs of the time spent by different grades of staff with the patient, of the consumable items used such as syringes, dressing packs and drugs, and of the investigations and treatments carried out during the admission were calculated. Finally, a cost was added for hospital services, using the part of the District Treasurer's figure for the cost per inpatient day that covers the costs of administration, medical records, catering, cleaning, laundry and hospital upkeep.

The costs for which a capital allocation or a service is provided by the Regional Health Authority have not been included. These are for blood transfusion and the capital costs of operating theatres and X-ray departments and their major items of equipment. The costs of outpatient attendances, other admissions and visits to general practitioners have also been excluded.

RESULTS

Length of stay for patients operated upon have been grouped into those having aorto-bifemoral grafts, femoro-popliteal grafts and "others" (Table I). "Others" include one patient having both operations, one having a renal artery graft in addition to an aorto-bifemoral graft, one having a femoro-femoral crossover graft and one having an amputation following the failure of a bilateral femoro-popliteal graft. The mean stay for the 13 patients having surgery was 13.7 days. Nine of these patients had separate admissions for angiography and assessment before admission for treatment, the mean stay for this being 3.2 days. Seven patients were admitted for assessment, catheter aortograms and balloon dilatation, with a mean stay of 3.4 days. Four patients were admitted for

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TABLE I

Length of stay of 24 patients admitted for investigation, surgery or dilatation

Admission for	No. of patients	Days in hospital		
		Total	Range	Mean
Surgery				
Aorto-bifemoral	6	81	11–17	13.5
Femoro-popliteal	2	29	13–16	14.5
Other	5	68	11–16	13.6
Total	13	178	11–17	13.7
Investigation				
+dilatation	7	24	2–4	3.4
Dilatation only	4	7	1–4	1.8

dilatation only, having been investigated either elsewhere or at a separate admission, and their mean stay was 1.8 days.

Costs are given separately at 1984 prices for staff and consumables for each department involved with the patients, except pathology, where a total cost is given (Table II). The patients having operations had aorto-bifemoral grafts in two cases and femoro-popliteal grafts in two cases. Two of the balloon dilatation patients had catheter aortograms at the time of dilatation, and one patient had a dilatation without an angiogram, that having been done elsewhere. Two patients admitted for investigation and catheter angiograms under local anaesthetic and one having a translumbar aortogram under general anaesthetic were also costed.

The mean cost of balloon dilatation was £301 per patient compared with £1328 for surgical bypass. Most of the cost difference was due to the shorter hospital stay and the lesser number of staff involved in dilatation under local anaesthesia compared with operation under general anaesthetic (Fig. 1). An aorto-bifemoral synthetic graft costs £128 compared with £70 for a balloon catheter for dilatation, and femoro-popliteal grafts were cheaper than aorto-bifemoral grafts because most are done using the patient's own vein. The cost of an anaesthetist and the stay in a recovery ward with an extra day in hospital was the main reason for the difference between the cost of a catheter and a translumbar aortogram.

Since patients admitted for non-urgent operation had

TABLE II

Mean costs for treatment and angiography, shown as costs for staff and consumable materials for each service used

		Surgery	Dilatation	Catheter aortogram	Translumbar aortogram
No. of patients		4	3	2	1
Mean stay (days)		13.0	1.7	2.0	3
Mean costs (£/patient)					
Physiotherapy:	staff	13.09	—	—	—
	consumables	0.14	—	—	—
ECG:	staff	0.50	—	0.80	0.91
	consumables	0.07	—	0.12	0.10
Vascular lab	staff	0.78	3.81	3.12	3.12
	consumables	0.03	0.21	0.14	0.12
Radiology (not angiography):	staff	1.58	—	—	—
	consumables	1.02	—	—	—
Angiography	staff	—	39.93	23.04	73.00
	consumables	—	133.36	77.35	80.09
Medical photography:	staff	0.46	—	—	—
	consumables	0.63	—	—	—
Ward:	staff	264.68	50.64	57.48	64.31
	consumables	88.38	0.94	1.10	0.90
Theatre.	staff	214.07	—	—	—
	consumables	139.72	—	—	—
Recovery/ITU.	staff	50.49	—	—	10.17
	consumables	12.70	—	—	3.55
Pathology (total)		38.76	6.83	7.85	8.84
Total staff cost		545.65	94.38	84.44	151.51
Total consumables cost		242.69	134.51	78.71	84.76
Hospital services (at £39.13/day)		501.02	65.22	78.26	117.39
Total		1328.12	300.94	249.26	362.50
(range)		(1613.93–827.93)	(267.17–347.84)	—	—

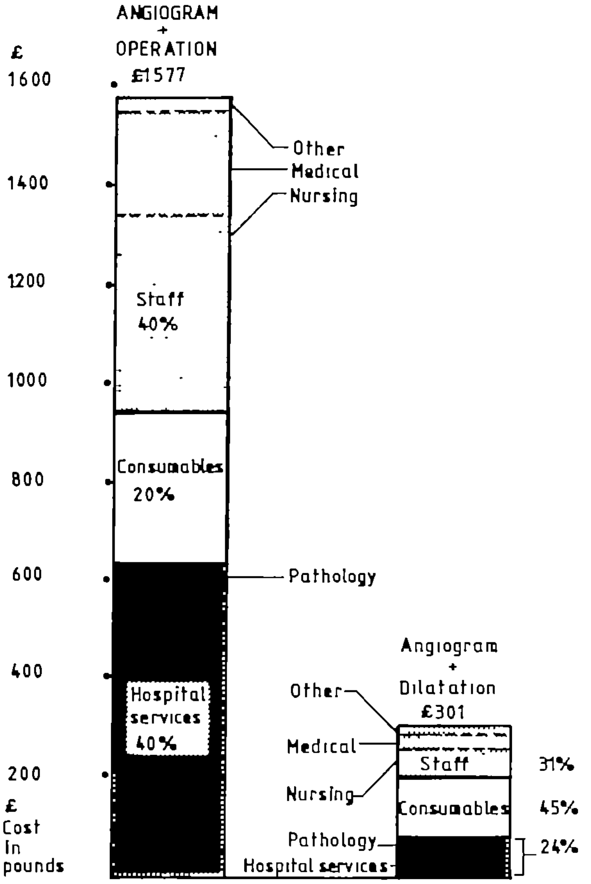

FIG. 1.

Comparison of the major components of the costs for patients having angiography and operation with those having angiography and dilatation.

a separate admission for investigation and assessment, the cost of £249 for that admission is added to the total cost of operation, bringing the mean cost of surgical treatment to £1577. Consumable items made up 20% of the cost of that treatment, while staff costs and hospital services (including pathology) each made up 40%. In patients having dilatations, the consumable items were a bigger proportion of the costs at 45% of the total, with staff costs being 31% and hospital services 24% of the total. In both methods of treatment the nursing costs were about 60% of the total staff cost.

DISCUSSION

Given similar patients in whom either surgery or dilatation is an equally acceptable treatment, and assuming that treatment is successful with both, dilatation appears to offer treatment at about one fifth the cost of operation. If dilatation is performed at the time of admission it adds between £50 and £100 to the cost of the admission, depending on how long the patient stays in hospital, but is more economical since it saves the costs of a second admission. A similar ratio of costs has been found in the USA (Doubilet & Abrams, 1984), although the total cost there is considerably higher. The total cost of an angiogram, calculated in a different way, in a hospital doing 60 each year, and allowing for a 10-year depreciation of capital costs, was found to be £288 (Stilwell, 1984). A similar allowance for the capital cost of the equipment used by us to do 500 angiograms annually would add £50 to the costs of each examination.

Other studies in which this method of costing was used have shown a cardiac valve replacement in Southampton in 1976 to cost £2037, and the costs of coronary artery bypass grafts in three different hospitals in 1980 to range from £2100 to £2507 (Mollo, 1982).

The process of costing is time consuming and expensive: the cost of this study was £5500. It may be asked if detailed costing is necessary, since approximate costs can readily be calculated from the hospital costs per inpatient day. In this hospital in 1982–83 this was £106.21, so that on the mean duration of admission that we found, the summated cost of surgery would be £1593 and £361 for investigation and dilatation. These figures are perhaps close enough for an overall comparison of the techniques, but hospital costs contain a number of assumptions, and it is reassuring to find that detailed costing of specific patients produces approximately the same result. Detailed costs have to be assessed if they are to be understood and controlled to use the available money to the best advantage. This study suggests that further savings could be made by altering the pattern of separate admissions for investigation and operation, possibly by deciding on the basis of outpatient vascular laboratory tests whether an operation will be needed. The costing has shown that, although successful dilatation is a relatively cheap procedure, it transfers some of the cost of treatment from the surgical to the radiological department. It has also become apparent that when a new technique is introduced the pattern of practice is changed, so that the direct calculation of technique costs does not reflect the overall change, and this has to be examined separately.

ACKNOWLEDGMENTS

We are grateful to all the staff and patients who cooperated in this study with such interest and enthusiasm, and to Mr R A. Saunders, the Regional Scientific Officer, for his support.

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MAY 1986

The effects of introducing balloon dilatation into vascular surgical practice

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ABSTRACT

The numbers of angiograms, balloon dilatations, reconstructive operations and amputations carried out annually over a 5-year period following the introduction of balloon dilatation have been counted and the change in estimated costs calculated. Over the 5-year period the numbers of angiograms and reconstructive operations carried out have doubled and the number of amputations has fallen from 52 in the first year to 39 in the fifth year. The number of dilatations has increased from six in five patients in the first year to 97 in 75 patients in the fifth year. The cost of investigation and treatment has doubled, but since more patients are being treated effectively, the mean cost per patient treated has fallen from £1855 to £1277. The introduction of balloon dilatation into vascular practice causes patients to be investigated earlier in the progress of their disease and enables more patients to be treated effectively with greater cost-efficiency, but does not reduce the overall cost of investigation and treatment of ischaemic disease of the lower limb.

It has been claimed that balloon dilatation of arteries or percutaneous transluminal angioplasty (PTA) for lower-limb ischaemic arterial disease is cheaper than operation and, when integrated with surgery, can give an improved outcome for the patient as well as reducing mortality and morbidity (Doubilet & Abrams, 1984). When the costs of PTA and reconstructive surgery are compared in a patient with a lesion that could be treated by either method, PTA is about one-fifth the cost of operation (Jeans et al, 1986). However, claims about the low cost of a new technique which alters the previous pattern of treatment without considering its effect on investigation and the overall treatment of the disease are likely to be misleading.

The introduction of PTA into vascular surgical practice may cause changes in the numbers of patients investigated, reconstructive operations performed and amputations carried out. We have, therefore, looked at these factors over a 5-year period to see what changes have taken place, and have estimated the ensuing changes in cost.

METHOD

The numbers of angiograms, operations and balloon dilatations performed each year at the Bristol Royal Infirmary for lower-limb ischaemia and the numbers of amputations carried out have been collected for the 5-year period 1980–84. Operations for aneurysms have been excluded.

The costs of the revascularisation procedures, angiograms and balloon dilatations have been calculated using the figures found in a study at the same hospital in 1984 (Jeans et al, 1986) and are based on 1984 values.

The consultant staff involved have remained the same throughout the period reviewed, with the exception of the retirement of one vascular surgeon who was replaced by another (M.H.).

RESULTS

Investigations

There has been a marked change in the method of angiographic investigation over the period, with a reduction in the numbers of translumbar aortograms (TLA) from 121 in the first to 42 in the fifth year, and an increase in the number of transfemoral catheter angiograms (TFLA) from two in the first to 178 in the last year (Table I).

Dilatations

These have increased from six dilatations in five patients in the first year to 97 in 75 patients in the fifth year.

Operations

Reconstructive operations have increased from 70 to 138 per year over the 5-year period. There has been a major increase in femoro-popliteal bypass grafts from 17 to 59 per year, with a moderate increase in femoro-femoral cross-over grafts from five to 17 per year. In spite of the increase in the number of patients investigated, there has been a 25% decrease in the number of amputations carried out, from 52 in the first year to 39 in the last year.

Costs

The total annual cost of investigation and treatment has risen over the 5-year period from £139 136 to £272 065 but, since the proportion of patients being investigated who are offered effective treatment by dilatation or operation or a combination of these has

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TABLE I

NUMBERS OF ANGIOGRAMS, RECONSTRUCTION OPERATIONS, DILATATIONS AND AMPUTATIONS PERFORMED ANNUALLY, 1980–84

	1980	1981	1982	1983	1984
Angiograms					
Translumbar	121	140	105	86	42
Transfemoral	2	9	46	126	178
Total	123	149	151	212	220
Balloon dilatations (no. of patients)	6 (5)	18 (18)	41 (32)	82 (67)	97 (75)
Operations					
Profundaplasty	6	8	15	21	11
Aorto-bifemoral	42	48	62	45	50
Femoro-popliteal	17	27	29	43	59
Femoro–femoral cross-over	5	4	11	9	17
Axillo-bifemoral	0	1	2	2	1
Total	70	88	119	120	138
Amputations	52	58	38	40	39

increased, the mean cost per patient treated has fallen in the same time from £1855 to £1277 (Table II). The changes in the factors examined over the 5-year period are shown graphically in Fig. 1.

DISCUSSION

These results show that the introduction of the new technique of PTA has caused a chain of effects, not all of which were expected. The increase in the number of angiograms follows the realisation that PTA allows atheromatous disease of the lower limbs to be treated earlier in the history of the disease, before the symptoms would justify surgery. Our criteria for investigation by angiography have now been extended to include patients with unilateral claudication having a fall in ankle pressure in the symptomatic leg on exercise, in addition to the longer-established indications. This approach is more likely to find those patients with the short iliac or superficial femoral stenoses in whom PTA is most successful (Johnston et al, 1982).

The cost of this increase in angiography has been partly offset by the change in the predominant method of investigation from translumbar aortography done under general anaesthetic, with a stay of 3 days, to transfemoral catheter angiography done under local anaesthetic, with a stay of 2 days. The single most important factor in determining the cost of hospital treatment is the length of inpatient care (Lamb & David, 1985) and any reduction in hospital stay will reduce costs. The number of patients having balloon dilatations has increased steadily and the smaller increase in the fifth year suggests that most of the potential demand in the district is now being met.

It was unexpected to find that the number of reconstructive operations had doubled over the 5 years, with the major increase being in femoro-popliteal bypass operations. The increase is a consequence of the policy of a more interventional approach to patients with pre-gangrenous ischaemia surgically as well as by dilatation.

TABLE II

COSTS TO NEAREST POUND OF INVESTIGATIONS, DILATATIONS AND OPERATIONS EACH YEAR AND COSTS PER PATIENT TREATED, USING 1984 COSTS

	1980	1981	1982	1983	1984
Angiograms					
Translumbar (as £362.50)	43 863	50 750	38 063	31 175	15 225
Transfemoral (at £249.26)	499	2243	11 466	31 407	44 368
Total	44 362	52 993	49 529	62 582	59 593
Dilatations (at £300.94)	1806	5417	12 339	24 677	29 191
Operations (at £1328.12)	92 968	116 875	158 046	159 374	183 281
Total cost of investigation and treatment	139 136	175 285	219 914	246 633	272 065
No. of patients treated	75	106	151	187	213
Cost/patient	1855	1654	1456	1319	1277

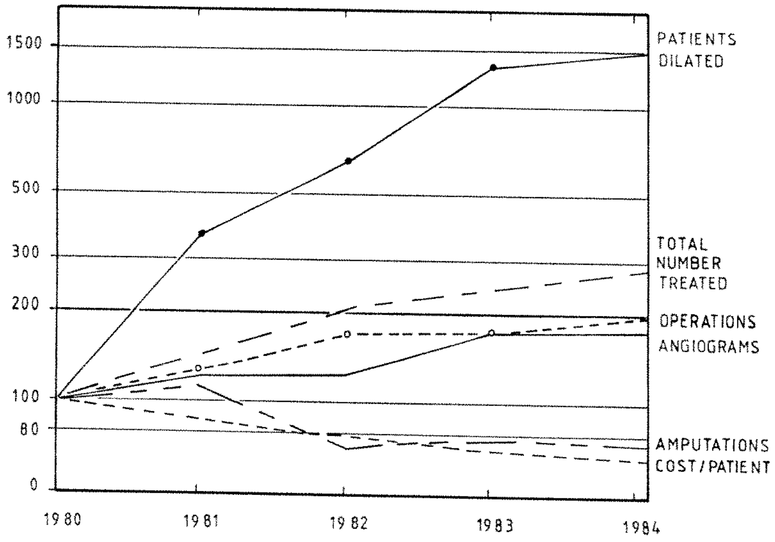

FIG. 1.

Standardised ratios (1980 = 100) to show the numbers of patients having angiograms, dilatations, amputations and reconstructive operations, with the mean combined cost of investigation and treatment per patient treated by PTA and operation, over the period 1980–84. The vertical axis is on a log scale.

Prior to the use of PTA the only effective treatment available for patients with ischaemic lower-limb disease was surgical. The advent of PTA appears to have almost tripled the numbers of patients being treated effectively so that, although the total cost of investigation and treatment over the period has doubled, the mean cost per patient has fallen by £578. The fall in the number of amputations also points to an improved service to the community, although we have not costed this.

We have not discussed the results in terms of cost-benefit (Pliskin & Taylor, 1977) since we do not yet have a 5-year life-table analysis of our results. Estimates suggest that iliac lesions have a 5-year patency of 63% for PTA compared with 89% for surgery, and femoral lesions a 5-year patency of 29% compared with 60% for surgery (Doubilet & Abrams, 1984). Failures of PTA in our hands are incorporated into our costings, since they went on to have surgery in the same hospital.

It appears from these results that the introduction of PTA increases the overall cost of investigation and treatment in ischaemic lower-limb disease because more patients are investigated and treated. This increased cost affects both the radiology department, since more investigations are requested and treatment is now carried out in selected patients, and the department of surgery, where more patients are being admitted for investigation and more operations are being performed. However, PTA is more efficient because it increases the number of patients having effective treatment and lowers the mean cost per patient treated. This is in addition to its established benefits of low mortality and morbidity, avoidance of anaesthetic risk and loss of sexual functioning, and its ability to be repeated without damage to veins which may be required for surgery later on at the same or another site (Johnston et al, 1982).

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We are grateful to Mr R. A. Saunders, the Regional Scientific Officer, for his support and to Mr E. Turnbull for Fig. 1.

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Book reviews

Some Issues Important in Developing Basic Radiation Protection Recommendations. NCRP Proceedings No. 6, Twentieth Annual Meeting, 4–5 April 1984. Ed by T. M. Koval, pp. 320, 1985 (NCRP, Bethesda), $19.00.
ISBN 0–913392–75–8

This booklet is virtually a verbatim version of the 1984 NCRP meeting, interesting to all involved in protection and risks, but published 18 months after presentation

The Taylor Lecture by Harold Rossi is included, though already published a year ago. There are many other interesting papers, beginning with a first-class overview by Schull and Weiss on the status of human risk assessment, using the latest Japanese mortality data from the 7th Life Span Study Report. The leukaemia experience seems now virtually complete, but the absolute risks for the solid cancers are still less certain or complete and the risks lower. Modifying factors, extrapolation models and future work are discussed. Other subjects include genetic and non-stochastic effects and pre-natal exposure

Another part of the meeting is more domestic, "What the NCRP should be doing for Federal Agencies", and there are also reports on selected NCRP activities, which include radiofrequency electromagnetic fields and mammography

As is usual, the general protection public could read this NCRP report with value and with thanks to the American taxpayer who subsidises it.

Keith E. Halnan

Radiation Protection in the Radiologic and Health Sciences, 2nd edit. Ed. by M E. Noz and G. Q. Maguire Jr, pp. xiv+277, 1985 (Lea & Febiger, Philadelphia), $27.00
ISBN 0–8121–0962–7

This paperback second edition of the book first published in 1979 is well written and easy to read. The authors open the book with a useful introduction of some 20 pages giving an outline of atomic physics. They then continue with a survey of radiation detectors, which is rather more detailed than is commonly the case in books on radiation protection, and there is a particularly useful account of the way in which scintillation detectors function A chapter on biological effects and what is called the maximum permissible dose equivalent (MPD) shows deviation from UK practice in that it implies that MPD values can be used to derive working standards, while in the UK, the dose equivalent limit is a legal limit of dose which, if exceeded, results in legal sanctions.

In the section on personnel monitors, it was surprising to find that it is considered possible that situations may still exist where there are high background levels which need to be identified with film dosemeters Environmental surveys with modern survey meters should locate such areas and the necessary measures can then be taken according to the ALARA ("as low as reasonably achievable") principle.

A particularly important chapter is devoted to protection principles governing diagnostic and oncological procedures with the subtitle of "Good working habits".

The book is aimed at students preparing for careers as medical physicists or health physicists, technicians in these fields and student radiologists. There is much to interest doctors or nurses concerned with radiation protection standards and techniques, but they may find the technological aspects best left to the physicists.

This is an excellent book from the point of view of the scientific and technological aspects of radiation protection and is to be recommended from this point of view. It gives less guidance on the human aspects of radiation protection, the chain of responsibility, nomination of responsible persons, the organisational structure which is required to manage a radiation protection programme and the education and counselling of all levels of staff, but no doubt these points will be dealt with in a future edition.

D. Gifford

Future Use of New Imaging Technologies in Developing Countries. Technical Report Series No. 723. Report of a WHO Scientific Group, pp. 67, 1985 (World Health Organization, Geneva), Sw Fr 7.00 (approx. £2.30).
ISBN 92–4–120723–X

This small book is the report of a group of radiologists from developing and developed countries which met in September 1984, with Professor Palmer of the University of California acting as chairman. It summarises the technical and cost factors of ultrasound and computed tomography and comments that the place of magnetic resonance imaging is unlikely to be established in this decade. The necessary background of training of clinicians, technicians and radiologists to use the techniques is discussed, together with the underlying requirements for stable electrical and water supplies for the equipment and the air conditioning needed for computed tomography It also emphasises the need for support from physicists and service engineers, so easily forgotten by civil servants in developing countries. The book then goes on to compare the two techniques and the clinical indications for their use, with a supporting list of 358 references.

The Scientific Group is to be congratulated on producing a clear, comprehensive and readable guide to the subject. It will be of help not only to countries or departments without these facilities, but is also an excellent introduction for anyone trying to decide which technique is applicable to a particular problem. I shall recommend it strongly to our FRCR students, from home as well as from overseas.

W. D Jeans

1986, *The British Journal of Radiology*, 59, 461–470

MAY 1986

In vivo evaluation of myocardial infarction by computed tomography: an experiment with electrocardiographic gating

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ABSTRACT

Retrospectively gated and ungated images of normal and 24 h post-infarction mini-pig hearts were obtained. The 11 imaged infarcts were produced by transcatheter embolisation of the branches of the left anterior descending coronary artery. Using a contrast infusion technique and scanning during infusion, four infarcts were clearly detected as low-attenuation areas in the myocardium, one of these showing adjacent contrast enhancement. Two other infarcts showed as enhancing regions. Two small infarcts (0.8–1.0 cm^3) were not detected and three others were in doubt. Streaking and other artefacts presented difficulties in image interpretation, which were sometimes resolved by gating. A comparison is made of these findings with those obtained from experiments with dogs, of comparable methodology. Differences are considered to result from anatomical differences between the two species, more particularly in the collateral blood supply to the myocardium.

Localisation and quantification of myocardial infarction are important both in clinical management and in prognostic assessment (Sobel et al, 1972). Accurate techniques for the measurement of infarction are likely to become more important with the increasing use of intervention. Computed tomography (CT) has been studied in the evaluation of experimentally produced myocardial infarction *in vitro* (Adams et al, 1976; Ter-Pogossian et al, 1976; Powell et al, 1977; Gray et al, 1978; Hessel et al, 1978; Higgins et al, 1979) and *in vivo* (Cipriano et al, 1981; Huber et al, 1981; Skioldebrand et al, 1981).

Electrocardiographically gated techniques have more recently been employed in attempts to extend the role of CT (Berninger et al, 1979; Doherty et al, 1981; Slutsky et al, 1983). Experimental data thus far, however, have all been obtained from the dog heart, which differs significantly from the human heart. Regional distribution of the coronary arteries is different (Lumb & Hardy, 1963); the collateral coronary circulation following infarction is relatively large (Blumgart et al, 1950) and the weight ratio of heart to body is higher in the dog than in the human. The pig heart is similar to the human heart in all these respects and is considered a more appropriate model of myocardial ischaemia for comparison with man (Savage et al, 1981).

The purpose of the present study was to determine the CT appearance of the normal anatomy and post-infarction changes in the mini-pig and to explore the possible advantage of an electrocardiographically gated technique in the early detection of infarction. The results are discussed in relation to data obtained from the dog and their clinical significance is considered.

MATERIALS AND METHODS

Investigation of normal anatomy

All studies were carried out in the University Department of Diagnostic Radiology. A total of 15 mini-pigs, in the 21–31 kg weight range, were studied using CT. The first six of the mini-pigs were used to determine the normal cardiac anatomy. Investigations employed with these animals were coronary angiography, CT coronary angiography and CT using either bolus or infusion techniques.

For all studies, the mini-pigs were first anaesthetised with intramuscular Immobilon (0.01 ml/kg). Each pig was intubated with a cuffed endotracheal tube and anaesthesia maintained by inhalation of fluothane (0.5–1.0%). Respiration was maintained with a Blease Manly ventilator and suspended in full inspiration during scanning. The heart rate was controlled at approximately 100 per min with intravenous atenolol (1–2 mg/kg). Ventricular arrhythmias were suppressed by intravenous lignocaine (0.2–0.4 mg/kg) in three pigs (Nos 6, 7 and 8).

Selective coronary angiography was performed in two animals under fluoroscopic control, utilising the transcarotid approach. Conventional plain-radiographic examinations were carried out and the animals were then transferred to the CT scanner. Computed tomographic angiography was performed at the mid-ventricular level as determined from an initial scanned projection radiograph. A 50:50 solution of saline and meglumine iothalamate (280 mg I/ml) was injected as a bolus at the start of scanning. A series of ungated mid-ventricular scans was then performed.

For all CT studies the mini-pigs were placed head-

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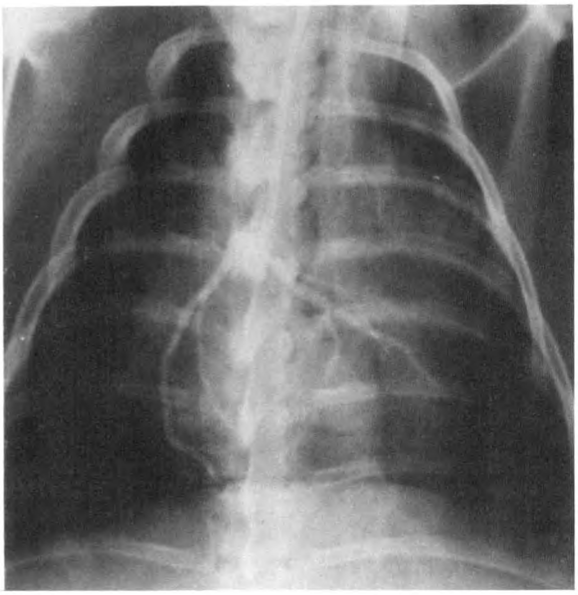


FIG. 1.

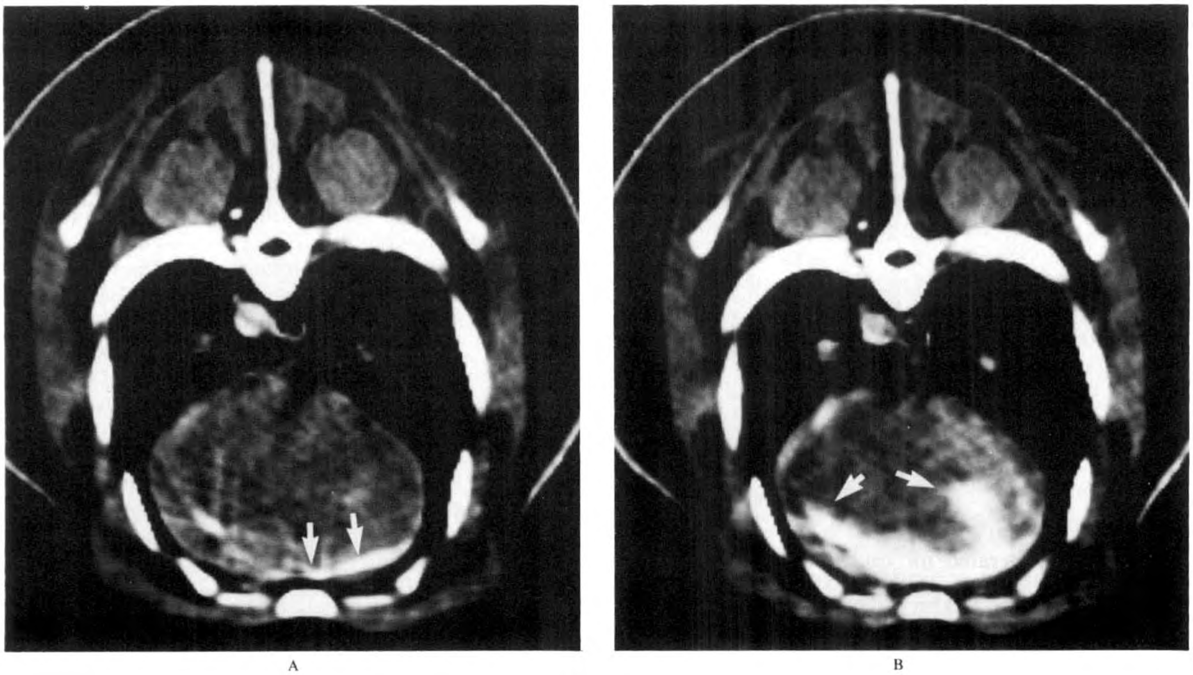
Results of coronary angiography in the normal pig. Contrast was injected simultaneously into the LAD and CX arteries.

first into the scanner in either the prone or right decubitus position.

The examinations were performed with an IGE CT/T 8800 scanner, incorporating a scan time of 5.6 s and an interscan delay time of 1.4 s. Scans of 1 cm thickness were obtained at 120 kVp and at the maximum mA allowed by the tube-cooling algorithm (normally 320 mA). A 320 × 320 matrix was used. The scanner was modified to permit retrospective electrocardiographic (ECG) gating, employing selected data from successive scans (Berninger et al, 1979). A gated image was reconstructed by the use of scan data acquired in relation to a retrospectively selected position (40% of the R to R time interval for systole and 0% for diastole) between consecutive R waves on the ECG trace. The gating window was approximately 100 ms. In order to obtain sufficient data to produce a gated image, six successive scans were performed at each level. Thus, a series of scans at each level required 41.8 s. Four levels at 1 cm intervals were normally necessary to survey the whole of the left ventricle. The time interval between scanning at each level was 1 min.

Post-myocardial infarction studies

Myocardial infarcts were successfully created in nine mini-pigs by embolisation with a copper coil (Kordenat



A

B

FIG. 2.

Ungated CT coronary angiography in the normal prone mini-pig. (A) The early phase following a bolus into the LAD and CX arteries. The positions of the arteries on the epicardial surface are shown (arrows). (B) The next slice in the same position, showing the regions of myocardium of the left ventricle, supplied by the combined LAD and CX, in the mid-ventricular region.

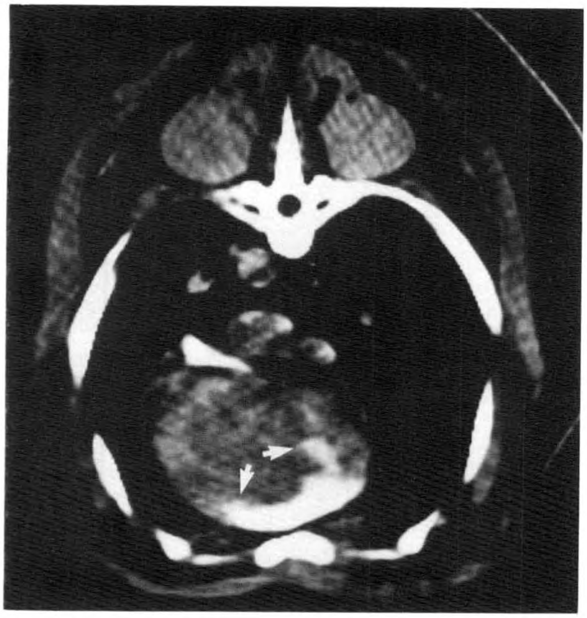


Fig. 3.

Ungated CT coronary angiography in a normal prone mini-pig following a bolus of contrast injected into the LAD artery alone. The region of myocardium supplied by the LAD is shown (arrows).

et al, 1972) through the left carotid artery. The coil was introduced into a branch of either the anterior descending (LAD) or circumflex (CX) branch of the left coronary artery. Two of these animals (Nos 3 and 9) received pre-infarct CT investigations.

The post-infarct CT examinations were performed 24 h after creating myocardial infarction. Both pre- and post-infarct scans were carried out with a contrast infusion technique employing meglumine iothalamate (280 mg I/ml) administered via a jugular catheter. For 10 min prior to scanning, contrast was delivered at 5 ml/min, using a B Braum-Melsungen AG pump. The rate was reduced to 2 ml/min during the CT study. Approximately 70 ml of contrast material (19.6 g I) was used during a typical examination.

The CT appearances were assessed on representative images from the display monitor using ×2 magnification, a window width of 150 HU and a window level of 90 HU. Electrocardiographically gated images were generated for each level and these were compared with the ungated images. Pre- and post-infarct images, where available, were also compared.

The experimental animals were sacrificed immediately after the post-infarction examination by an overdose of sodium pentobarbital. The heart was removed from the thorax and sectioned at 1 cm intervals in planes comparable with the CT images. The slices were incubated in a solution of nitroblue tetrazolium containing a phosphate buffer for 15 min at a pH of 7.4, thereby staining only the normal myocardium (Brody et al, 1967). Each unstained region of infarction was dissected from the slice and placed in a 10 ml measuring cylinder containing 5 ml of water. A measure of total infarct volume was obtained by water displacement.

Results

The normal mini-pig left coronary arteries, as demonstrated by angiography, are shown in Fig. 1. The CT equivalent in the same animal is shown in Fig. 2. The highlighted region of myocardium (Fig. 2B) resulted from the simultaneous infusion of contrast medium into the CX and LAD arteries. The result of selective catheterisation of the LAD artery in a different animal is shown in Fig. 3.

An example of the normal CT cardiac anatomy, at the four levels covering the left ventricle, is shown in Fig. 4. The ungated images are selected from those six gained at each level. The systolic and diastolic images obtained from the gated reconstructions are shown at each level using the infusion technique. The status of the mini-pig myocardium could only be assessed realistically in the two 1 cm-thick central axial sections shown in Fig. 4 (B and C). The sections to either side (A and D) of these were often subject to partial-volume artefacts produced by curvature of the myocardium. The combination of CT angiography (Figs 2 and 3) and the location of infarcts at post-mortem examination allowed the reconstruction of regional blood supply in this mid-ventricular region (Fig. 5).

Further differentiation of normal anatomical structures can be obtained by bolus injection during CT at any one level (Fig. 6). This technique, however, requires careful timing of the bolus: it can produce marked streaking, it does not lend itself readily to observation of multiple levels and it can give rise to a patchy myocardium (Doherty et al, 1983). For these reasons, bolus injection was abandoned in favour of the infusion, steady-state approach.

Myocardial infarction

Eleven infarcts (nine transmural and two subendocardial) measuring 0.2–10.1 cm^3 were identified in the nine pigs at post-mortem examination. In two pigs (Nos 5 and 8), due to technical problems, two copper coils were released, resulting in two regions of infarction in each pig. Infarcts were situated in the territory of the CX artery ($n = 5$), the LAD artery ($n = 5$) and the diagonal branch of the LAD ($n = 1$) (Table I).

Four of the 11 myocardial infarcts (all transmural) were clearly demonstrated as low-attenuation areas on CT. One of these showed adjacent contrast enhancement (Fig. 7). Two other infarcts showed as enhancing areas; one enhanced fully, one partially. Two infarcts were not detected on CT and three were doubtful. Those not detected were small in volume

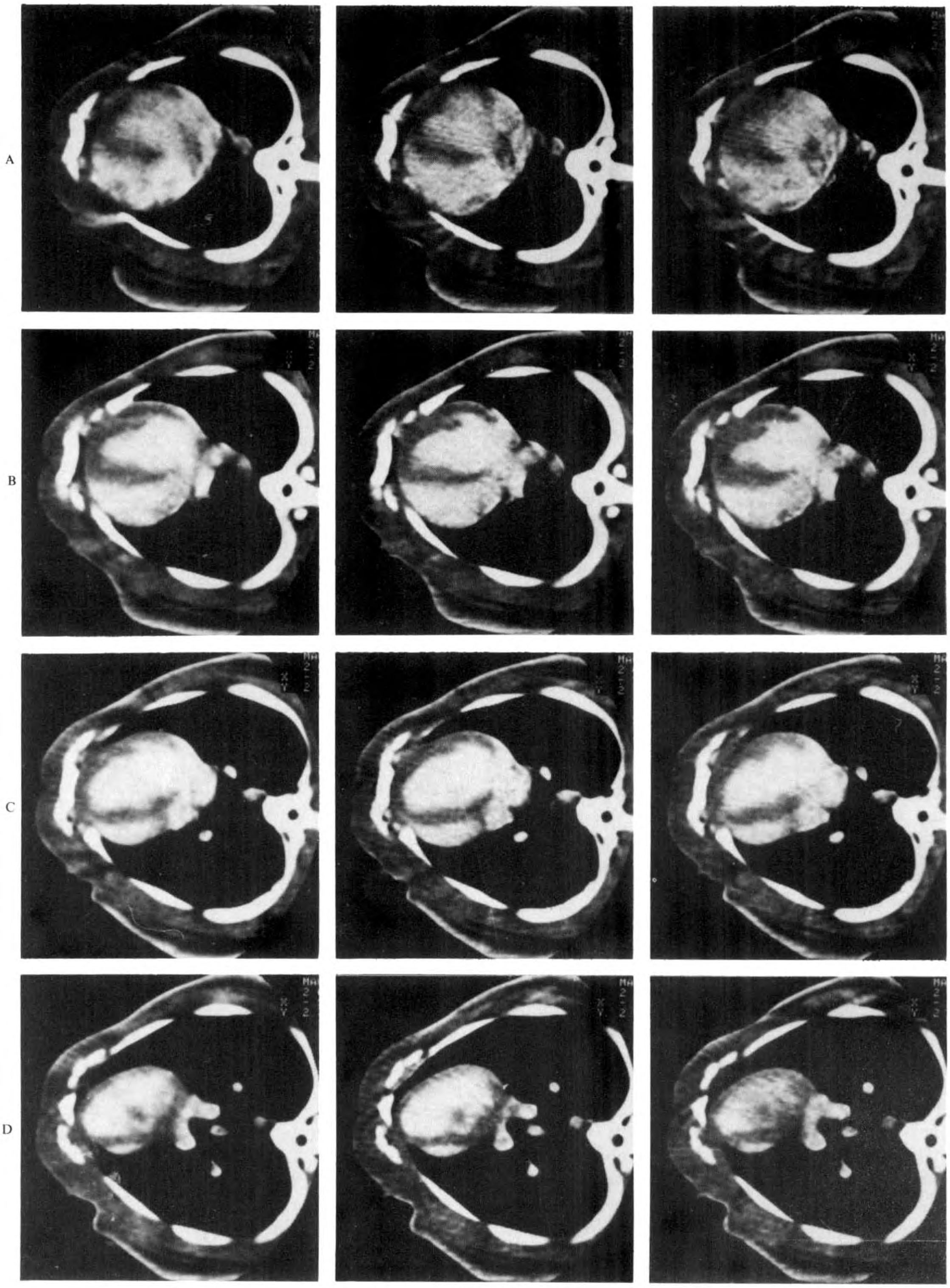


FIG. 4.

The normal CT anatomy of the lateral decubitis mini-pig in the four 1 cm slices (A to D) covering the full extent of the left ventricle. A selected ungated image and the two gated images, are shown for each level. The left hand image in each row is ungated, the central image is gated diastole and the right, gated systole.

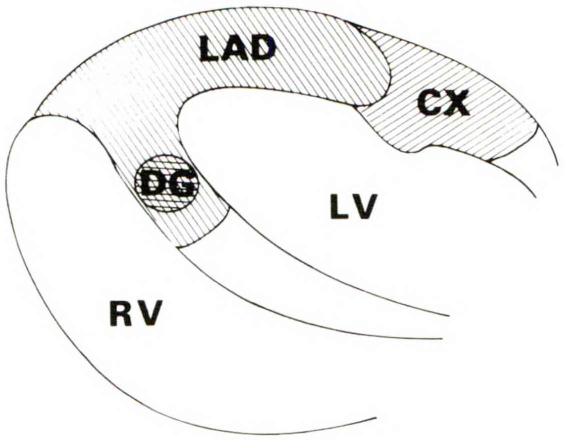


FIG. 5.

Diagrammatic presentation of mid-ventricular CT section in a normal lateral decubitis mini-pig, showing regional blood supply. The left and right ventricles (LV and RV) are shown. The myocardial regions supplied by the LAD and its diagonal branch (DG) plus the CX are outlined.

TABLE I

INFARCT SITE, TYPE AND APPEARANCE IN NINE MINI-PIGS

Pig	Region of infarct	Type of infarct	CT appearance	Infarct volume post-mortem (cm^3)
1	CX	TM	No infarct seen	1.0
2	CX	SE	No infarct seen	0.8
3	CX	TM	Low-attenuation area	4.5
4	LAD	TM	Doubtful low-attenuation area	5.0
5	LAD	TM	Margin contrast enhancement	5.2
	DG	TM	Full contrast enhancement	0.8
6	CX	TM	Low-attenuation area	10.1
7	LAD	TM	Low-attenuation area	5.7
8	LAD	TM	Doubtful low-attenuation area	3.9
	CX	SE	Doubtful low-attenuation area	0.2
9	LAD	TM	Low-attenuation area	—

DG = diagonal branch, TM = transmural, SE = subendocardial.

(0.8–1.0 cm^3), but the three in doubt varied in size (0.2–5.0 cm^3).

Figures 8, 9 and 10 show three cases of infarcts successfully detected in ungated CT images, their equivalent systolic and diastolic gated images and the corresponding pathological sections stained with nitroblue tetrazolium. The low-attenuation areas in the CT images appeared to be smaller than the unstained pathological regions of infarction.

Ungated CT images obtained from normal mini-pig hearts were less prone to "streaking" than those obtained from infarcted hearts. The most successful gated images were obtained from normal hearts (see Fig. 4). Gated images from infarcted tissue showed little difference in wall position between systole and diastole, were frequently noisy and were often degraded by artefact. One infarction resulted in a large inverted T wave on the ECG trace which could not be distinguished from the R wave by the available software. This resulted in an incorrect estimate of the R to R interval and inappropriate view selection in the gating reconstruction. In three animals (none of which

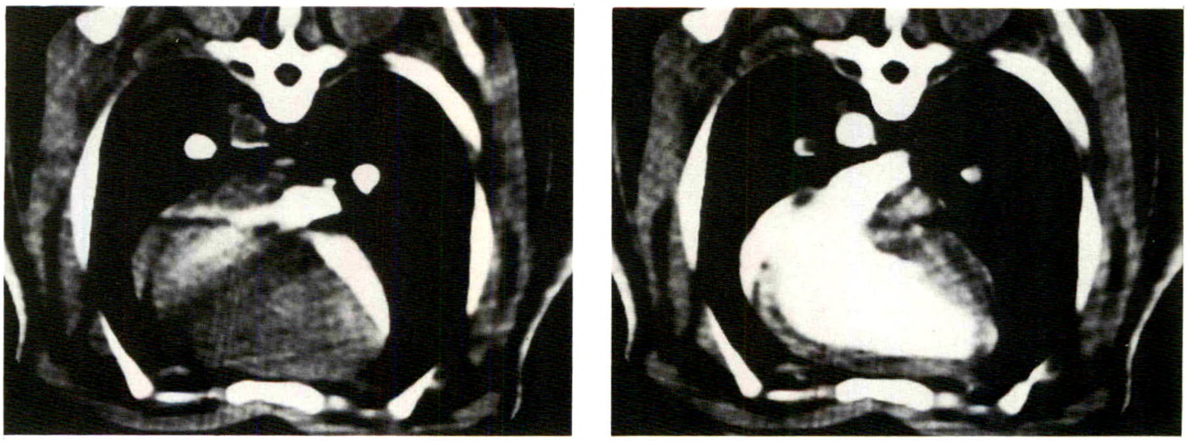

A B

FIG. 6.

Ungated images resulting from a bolus technique in a normal prone mini-pig. (A) The right heart chambers. (B) The left heart chambers. "Streak" artefacts are one of the many problems with this technique.

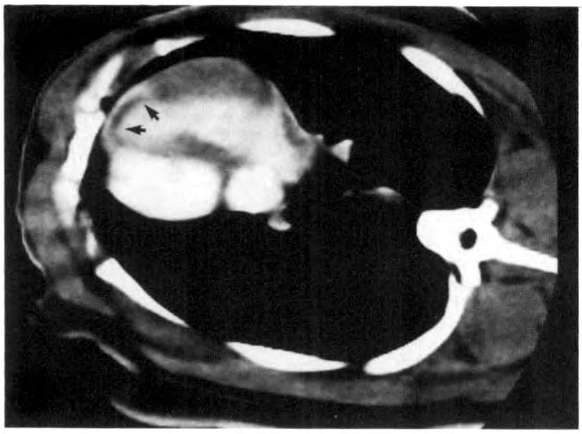


FIG. 7.

A systolic gated image for mini-pig No. 9 scanned in the lateral decubitus position 24 h post-LAD embolisation. A low-attenuation region (arrows) is surrounded by an enhancing epicardial rim, at the apex of the left ventricle. Contrast medium pooling in the dependent right side of the heart is due to pulmonary congestion.

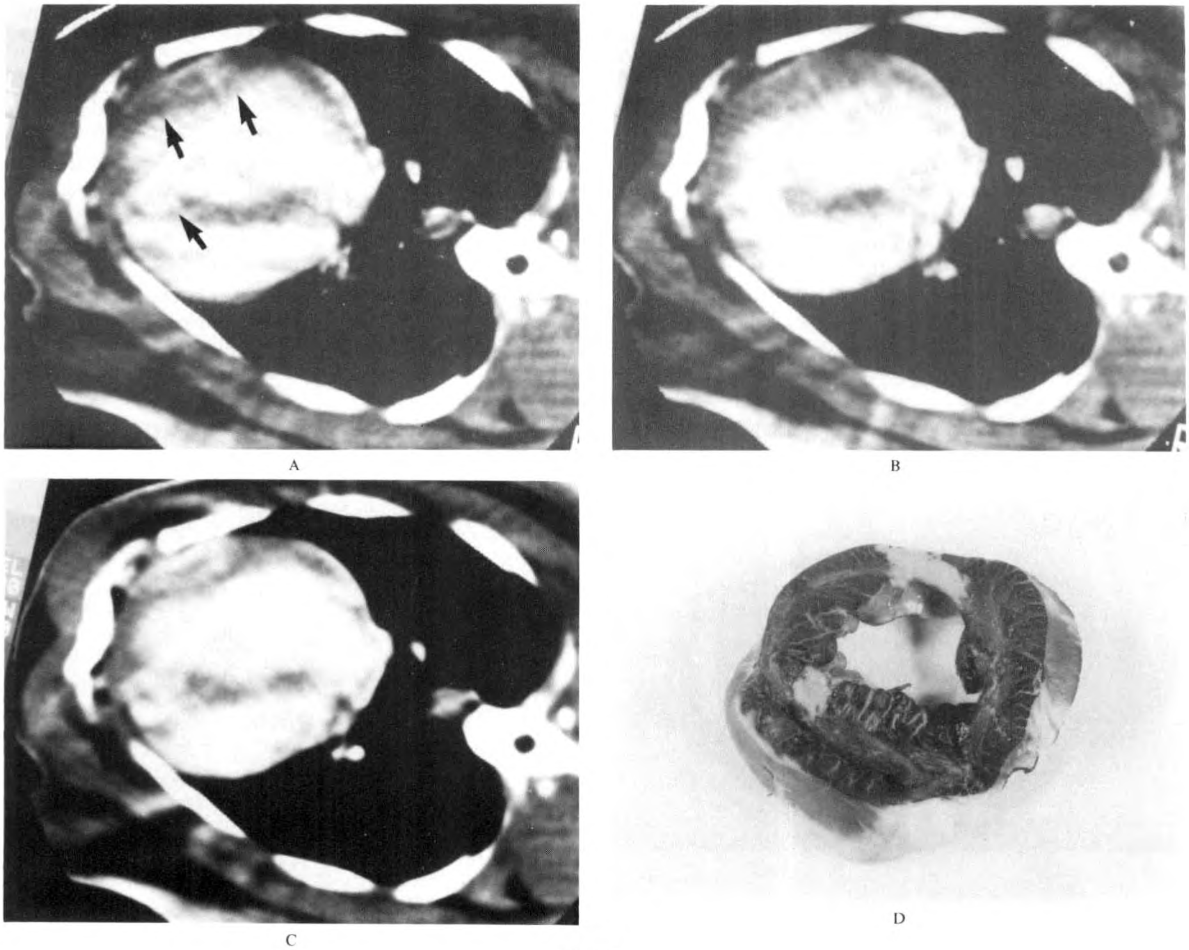
had lignocaine) frequent arrhythmias mimicked R waves and prevented appropriate view selection.

The five infarcts either not demonstrated or doubtfully demonstrated on ungated CT were no more clearly identified on gated CT. In two of these five cases, gating was unsuccessful due to arrhythmias. In only two cases (Nos 5 and 6) was gating helpful in the identification of infarction. In these cases certain artefacts were less pronounced in the gated images (see Figs 8 and 9).

DISCUSSION

The copper coil embolisation technique (Kordenat et al, 1972) occasionally caused streaking because of the coil lodging in the central myocardial region. Although a limitation of the technique, this was not the main cause of streaks, which, together with other artefacts in the heart images, made precise identification of infarcted areas difficult and precluded useful numerical analysis of the infarcted zones.

Artefacts in heart images have been discussed only briefly by other authors (Doherty et al, 1983; Oyama et al, 1984). We do not believe that the images presented



A

B

C

D

FIG. 8.

Two gated (A and B) and an ungated image (C) for mini-pig No. 5 scanned (lateral decubitus) at 24 h. The comparable, stained pathological section is shown (D). Two areas of infarction are visible, one area of marginal enhancement (two arrows) and a second region of complete enhancement (single arrow). Both areas correlate well in size with the pathological findings. The completely enhancing region is clearer in the gated images.

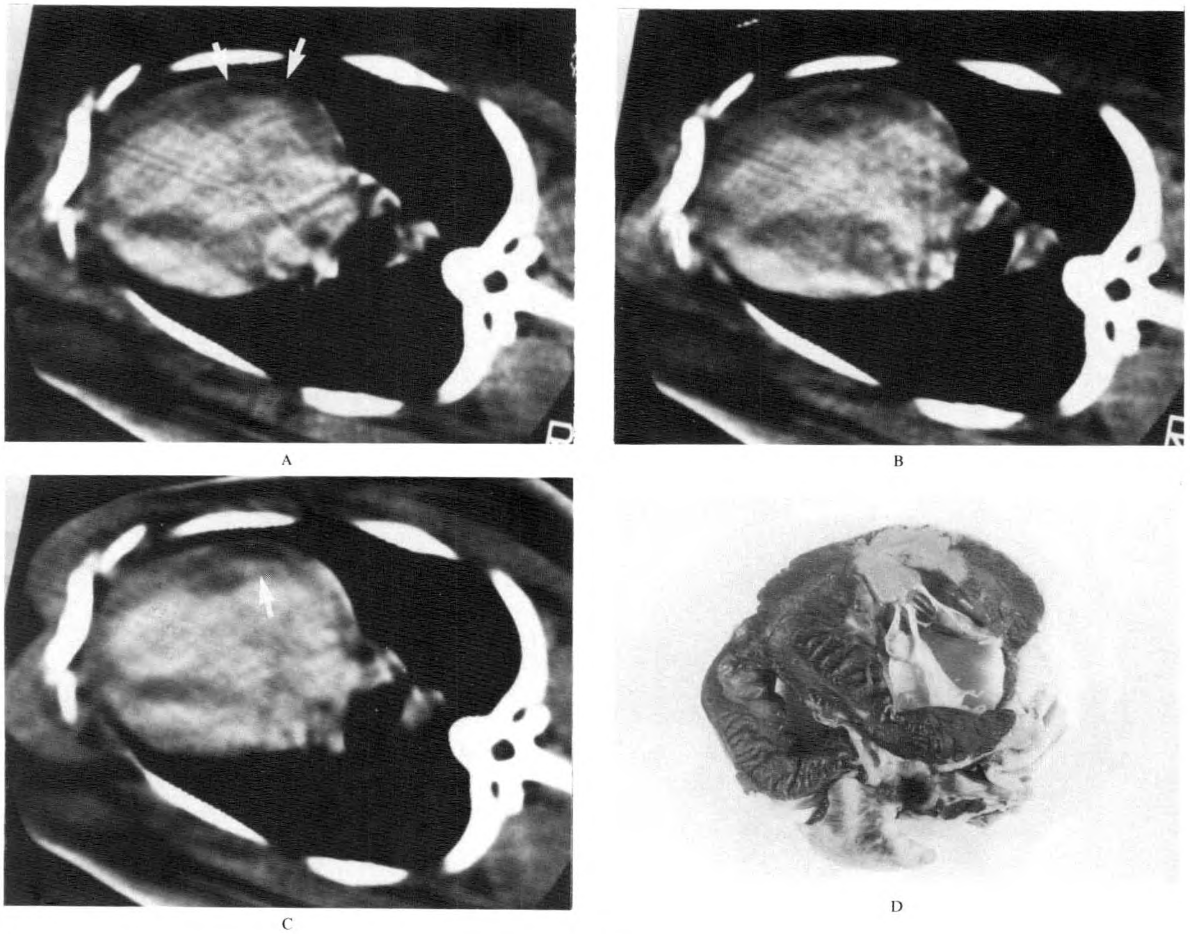


FIG. 9.

Two gated (A and B) and an ungated (C) image for mini-pig No. 6 scanned (lateral decubitus) at 24 h. The comparable stained pathological section (D) is shown. The consistently low-attenuation region (two arrows) is smaller than the area of infarction seen in the specimen. The apparent endocardial enhancement noted in the ungated image (single arrow) is not present in the gated images.

here are particularly better or worse than others reported. In all images there were streak artefacts, made more or less evident by window settings. These streaks can be of either high or low attenuation (see first slice, Fig. 4) and can generate either high- or low-attenuation bands or blocks in the myocardium. To be certain that a low- or high-attenuation area was not an artefact, the full series of six images at any one level had to be examined with care. During the process of careful image assessment, varying the window settings was useful for individual images, but fixed window values were essential for comparison between animals.

Figure 11 shows two series of images, made before and after infarction. In the pre-infarct images the variability of the streak artefacts and their effect on the septum can be seen clearly.

Other artefact problems include the confusion of epicardial blood vessels with marginal infarct enhancement. The early phase of the CT coronary angiogram (Fig. 2A) shows the position of these epicardial vessels. Also, contrast-medium pooling in either ventricle can be mistaken for enhancement on the endocardial surface of an infarct. Such artefacts can, on occasion, be resolved by the generation of gated images as shown in Figs 8 and 9.

The small, completely enhancing infarct seen in mini-pig No. 5 (Fig. 8A) could have been a case of marginal enhancement obscured by partial volume and machine-dependent error, *i.e.* the point spread function. Low-attenuation central regions may not be resolved in infarcts the same size as or smaller than the slice thickness.

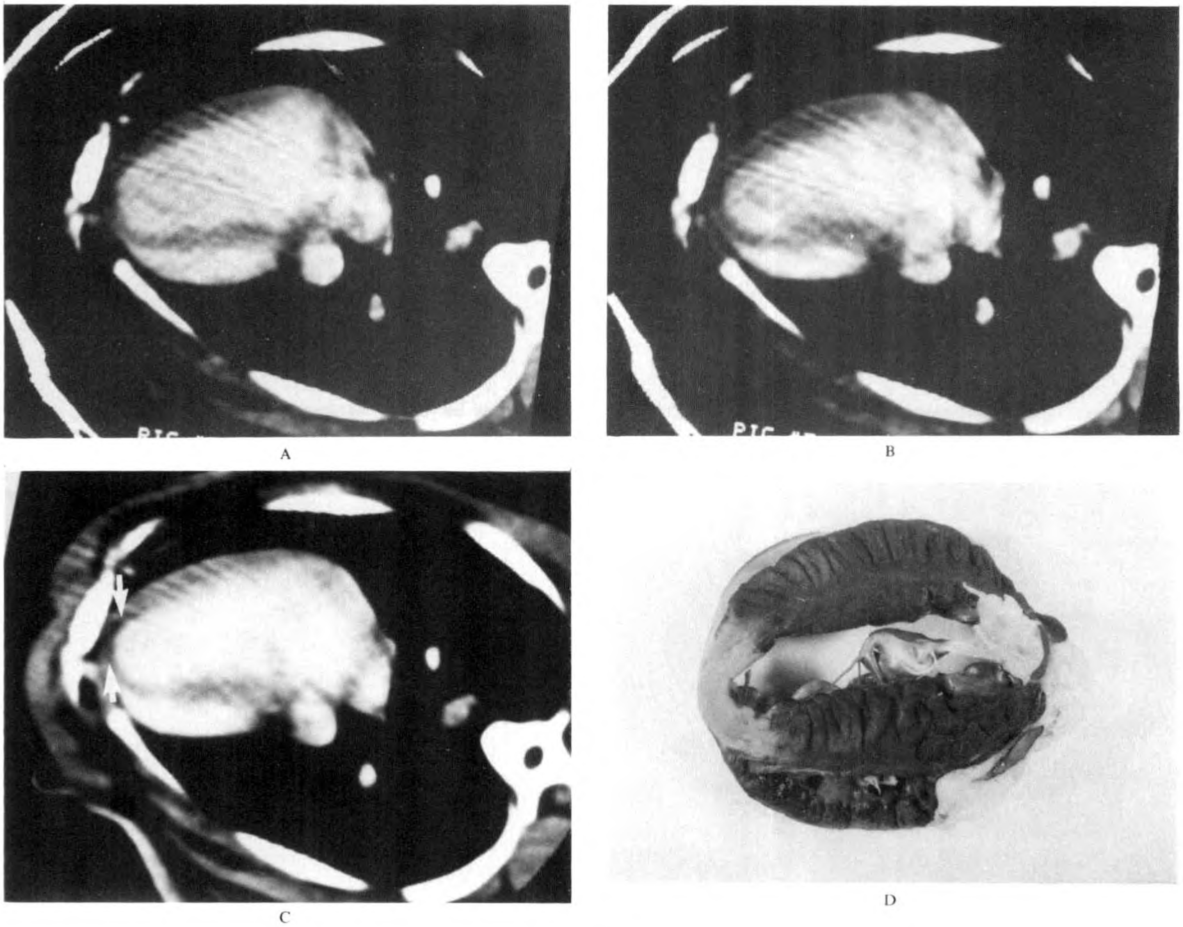


FIG. 10.

Two gated (A and B) and an ungated (C) image for mini-pig No. 7 scanned (lateral decubitus) at 24 h. The comparable stained pathological section (D) is shown. The low-attenuation infarct area (white arrows) appears smaller than the infarct visible in the specimen.

The present study has shown differing accumulation of intravenously administered iodinated contrast material in normal and infarcted myocardium (Table I). Transmural infarcts ranging in volume from 0.8 cm^3 to 10.1 cm^3 have been identified as both low-attenuation and enhancing areas on the CT images. Such appearances have been reported previously in both the dog (Doherty et al, 1981; Higgins et al, 1982; Slutsky et al; 1983) and the human (Lackner & Thurn, 1981; Carlsson et al, 1982; Oyama et al, 1984). A close examination of the techniques employed is, however, necessary before any comparison between CT images of different species can be made.

In the dog, those studies using a bolus technique (Ter-Pogossian et al, 1976; Hessel et al, 1978; Cipriano et al, 1981) must be excluded as being radically different in method from the steady-state infusion used in this study. Similarly, infarcts of a different age from those studied here (24 h) cannot be compared, since age of infarct has been shown to affect the contrast-enhanced CT appearance (Ringertz et al, 1983). Timing of the scan relative to the infusion can also influence infarct appearances (Ringertz et al, 1983). Comparison must, therefore, be restricted to images obtained during the period of infusion.

The most significant anatomical difference between the dog and the pig is an extensive coronary collateral circulation present in the dog but not in the pig. Two groups of investigators (Higgins et al, 1982; Ringertz et al, 1983) have, in the process of producing myocardial infarction in the dog, occluded the collateral vessels, Such models are perhaps closest to the pig and the grey appearance of the so called "dense" dog infarcts is similar to the appearances observed in this study. Ringertz et al (1983) scanned dogs immediately following contrast infusion. In the dense infarcts both

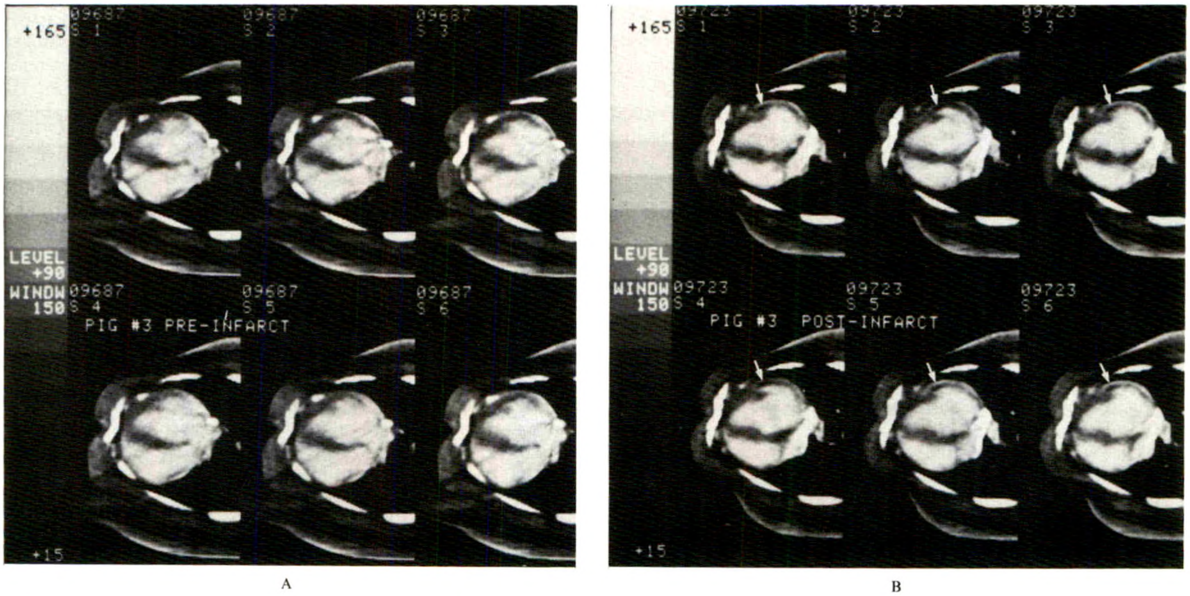


FIG. 11.

Two series of lateral decubitus scans carried out on mini-pig No. 3. (A) Pre-infarct, (B) post-infarct. Note the variability in the appearance of the myocardium between scans in each series. The low-attenuation CX artery infarct area (white arrow) is, however, present in all six post-contrast scans.

low-attenuation centres and marginal enhancement were observed; results similar to those reported here. These data may be compared with those obtained by Doherty et al (1981) for the normally collateralised 24 h dog infarct. Using an infusion procedure virtually the same as that employed in the present study, only low-attenuation or "filling defect" areas during the period of infusion were noted.

The presence of marginal enhancement in the pig and in "dense" dog infarcts may be explained on the basis of the residual blood flow to the infarct margin. In the pig, 24 and 48 h after infarction (Savage et al, 1981), marginal blood supply was 91% and 81%, respectively, of pre-occlusion flow. In the dog at 48 h (Higgins et al, 1982), residual blood flow at the margin of the infarction was 36% of normal, increasing to 46% of normal in the dense (non-collateral) infarcts. Residual blood supply to the margin of the infarcts appears, therefore, to have an inverse relationship to the presence of collaterals.

The presence of collaterals in the human suffering from myocardial infarction is a function of the ischaemic history. If the presence of collaterals, residual blood supply and marginal enhancement are related, then the varied CT enhancement observed in human myocardial infarction could be explained. The ideal model of human infarction might be the mini-pig heart infarcted after a period of reduced flow sufficient to produce the appropriate degrees of collateral development.

CONCLUSIONS

The detection of myocardial infarcts using contrast-enhanced CT techniques suffers from many artefact complications and great care is, therefore, necessary in the interpretation of the images. Gating appears to offer limited advantages over ungated imaging.

Marginal infarct enhancement was present in the pig, but has not been found in the dog under similar experimental conditions. This may relate to the presence of a decreased marginal blood supply in the highly collateralised dog myocardium as compared with the pig. The apparent contradiction in this conclusion could be explained by the presence of a more marked, collateral-induced, post-infarct oedema in the dog, equivalent to that found in reperfusion experiments.

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A rational approach to the investigation of the gallbladder

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ABSTRACT

A technique for the investigation of suspected non-acute gallbladder disease is described. It is based on properly conducted oral cholecystography (OCG) augmented, when necessary, by ultrasonic examination of the gallbladder (UCG) during the patient's same visit. This regimen has been applied successfully for 5 years; the results of a recent year's work are presented and discussed. Only 12.2% of patients required both investigations and, using the OCG technique described, in only 1.1% of cases was the gallbladder inadequately opacified when subsequent UCG was normal. This approach involves no increase in work-load and provides the referring clinician with objective evidence of the presence or absence of disease following a single visit by the patient to the X-ray department.

The incidence of cholecystectomy in the West is increasing (Plant et al, 1973; Fowkes, 1980). It has been estimated that the operation is performed on over 25 000 women annually in England and Wales (Layde et al, 1982). The morbidity and mortality associated with cholecystectomy are not inconsiderable and, therefore, accurate pre-operative assessment is essential. Oral cholecystography (OCG) has been widely used for many years. Ultrasonic examination of the gallbladder (UCG) was introduced as a complementary test with the advantage of being independent of gallbladder function. Recently, it has been suggested that UCG should replace OCG as the initial investigation (Cooperberg & Burhenne, 1980; Detwiler et al, 1980; McIntosh & Penney, 1980; Hessler et al, 1981; de Lacey et al, 1984). The logistic problems of this latter approach prompted us to devise a rational method of investigation in suspected non-acute gallbladder disease. This combines the benefits of well conducted OCG with, if required, subsequent high-quality real-time UCG. The aim is to provide the referring clinician with objective evidence of the presence or absence of disease following a single visit by the patient to the X-ray department.

The regimen described here has operated successfully for nearly 5 years and we report a retrospective study of a recent year's work.

PATIENTS AND METHODS

Control radiographs of the gallbladder were not obtained. Following referral to the X-ray department for investigation of suspected gallbladder disease, patients were given 12 500 mg tablets of iopanoic acid (Sterling Research Laboratories) together with instructions for a high-fluid, fat-free diet on the day prior to the examination. Patients were instructed to take four tablets with each of the three main meals on that day, followed by only clear fluids after the evening meal. Patients attended for radiography at 9.00 a.m. the next day. Compression fluoroscopy of the gallbladder was performed by a radiologist with the patient in the erect position and spot films were obtained. Routine, "after fatty meal" films were not obtained, fat being given only when there was a specific indication. Oral cholecystography was performed by a consultant radiologist or a registrar in training. Examinations by registrars with less than 2 years' experience were checked by a consultant.

The OCG results were categorised into four groups (Table I). No further tests were performed on patients in Groups 1 and 2. Patients in Groups 3 and 4 were referred for immediate UCG, performed by a radiologist using commercial real-time sector scanners with 3.5 MHz and 5 MHz transducers. Patients were examined in the supine, right anterior oblique and, if necessary, erect positions.

In a 12-month period (January—December, 1984), 402 patients attended for OCG. Fifty patients were excluded from the study for various reasons (Table II). Of the remaining 352 patients, 224 were referred by general practitioners, 119 from hospital outpatient departments and nine hospital inpatients. There were 263 females and 89 males. The mean age was 46 (range 15–87) years.

TABLE I

CATEGORIES OF RESULTS OF OCG IN 352 PATIENTS

Group		No. (%) of patients
1	Adequate opacification and visualisation of gallbladder and no abnormality demonstrated	262 (74.4)
2	Adequate opacification and visualisation of gallbladder, diagnostic of gallbladder disease	47 (13.4)
3	Adequate opacification of gallbladder but visualisation of gallbladder impaired by bowel contents	10 (2.8)
4	Inadequate opacification of gallbladder	33 (9.4)

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TABLE II

REASONS FOR EXCLUSION FROM STUDY (50 PATIENTS)

Reason for exclusion	No. of patients
Previous UCG	33
Previous OCG	13
Failed to follow instructions	2
Ultrasonic examination of the gallbladder booked for same morning	1
Followed instructions but refused to be exposed to X rays	1

RESULTS

The results of OCG are given in Table I and the range of abnormality demonstrated by OCG are given in Table III. Of the 10 patients in Group 3 (Table I), one left the X-ray department before the OCG films had been viewed and was subsequently lost to follow-up; UCG was performed on the remaining nine. Three (33%) were normal and in six (67%) cholelithiasis was demonstrated. All 33 patients in Group 4 underwent UCG (Table I). Four (12.1%) were normal, in 27 (81.8%) cholelithiasis was demonstrated and in two (6.1%) thickening of the gallbladder wall without calculi was demonstrated (Table IV).

DISCUSSION

In our department a system of investigation of the gallbladder has evolved which is based on fluoroscopically controlled OCG with erect compression films followed, when required, by real-time UCG. Cholecystograms are included in upper gastrointestinal screening sessions and the whole procedure, including obtaining spot films,. takes only 2–3 min. The ultrasound examination takes 4–5 min and is performed immediately on patients requiring it, obviating separate appointments.

The aim of providing a single-visit investigation of the gallbladder, using OCG, precludes obtaining a control radiograph, but the latter are rarely of value except in children (McAlister et al, 1978; Andersen & Madsen, 1979).

Compression fluoroscopy of the gallbladder with spot films using a horizontal beam are essential for good OCG technique (Lubert & Krause, 1953; Dodds & Mani, 1970; Dodds & Stewart, 1977). Often, when UCG has been compared with OCG, the method of OCG either has not been described or has been less than ideal. When attempts to assess the accuracy of OCG have been made, different results have been obtained. Comparisons of OCG with pathological examination of the gallbladder have found OCG to be in error in as few as 1.9% and as many as 48.8% of cases (Baker & Hodgson, 1960; Athey & Martinez, 1979).

TABLE III

ABNORMALITIES DEMONSTRATED IN GROUP 2 (TABLE I) (47 PATIENTS)

Abnormality	No. (%) of patients
Cholelithiasis	43 (91 5)
Cholelithiasis + adenomyomatosis	1 (2.1)
Adenomyomatosis	2 (4 3)
Cholesterol polyps	1 (2.1)

TABLE IV

RESULTS OF UCG IN GROUP 4 (TABLE I) (33 PATIENTS)

Results of UCG	No. (%) of patients
No abnormality demonstrated	4 (12.1)
Cholelithiasis	27 (81 8)
Thickened gallbladder wall without calculi	2 (6 1)

The main criticism of OCG is the failure of the contrast medium to opacify adequately a significant proportion of normal gallbladders. After a standard dose of 3 g iopanoic acid, inadequate opacification of the gallbladder has occurred in up to 16.6% of cases. Performing repeat OCG using the same dose of iopanoic acid has shown that up to 30.3% of the gallbladders that initially failed to opacify adequately were normal. Thus, of all the patients given 3 g iopanoic acid, up to 5% will have a normal gallbladder that will fail to opacify satisfactorily (Rosenbaum, 1959; Berk, 1970). Studies giving a double dose (6 g iopanoic acid) over 48 h have shown that opacification was inadequate in between 3.1% and 11.7% of cases. Inadequate opacification was shown to be associated with pathology of the gallbladder in between 63.2% and 78.6% of these cases (Burhenne & Obata, 1975; Burhenne et al, 1981). As the peak opacification of the gallbladder occurs 14–19 h after ingestion of iopanoic acid (Whalen et al, 1972), it is logical to give a double dose over 24 h. In our experience, this regimen resulted in inadequate opacification of the gallbladder in 9.4% of cases and in only 12.1% of these was the subsequent UCG normal. Thus, in only 1.1% of all our cases was opacification of the gallbladder inadequate with subsequently normal UCG. We consider that this result more than offsets the small extra cost of giving every patient 6 g iopanoic acid. Iopanoic acid causes more mild diarrhoea than other contrast media (Healey & Grainger, 1965; Fielding & Whitehouse, 1979). We noted an increase in the number of patients experiencing mild diarrhoea but this did not prove to be a significant problem.

Although recent series comparing OCG and UCG suggest that the tests are equally effective (Detwiler et al, 1980; Krook et al, 1980; de Lacey et al, 1984), some authors suggest that UCG should now be the initial test (Cooperberg & Burhenne, 1980; McIntosh & Penney, 1980; Hessler et al, 1981). Further studies supporting this approach advocate, in addition, the use of OCG where UCG has been normal (Detwiler et al, 1980; de Lacey et al, 1984). An assessment of this approach showed that it was necessary for all patients to take OCG contrast medium and that most patients (71.2%) require both tests (de Lacey et al, 1984). Our regimen resulted in only a small number (12.2%) of patients requiring both tests. In many hospitals this would solve the logistic problem of radiologists performing UCG on large numbers of patients. Oral cholecystography depends entirely on the functional integrity of the liver and gallbladder, while UCG provides purely anatomical information. Because each test is based on completely different parameters, if only one test is employed, there will always be a group of patients with equivocal results requiring a second test. However, in any investigation it should not be necessary to confirm all normal results (Detwiler et al, 1980; de Lacey et al, 1984), any more than it is necessary to confirm all abnormal results.

In a small number of patients, UCG is recommended as the initial investigation of suspected non-acute gallbladder disease. Pregnant patients should not be exposed to X rays. Where there is a history of a severe reaction to iodine-containing contrast media, OCG is contraindicated. However, OCG is accurate and suitable for the majority of patients and, where medical dissolution therapy for cholelithiasis is considered, OCG gives necessary functional information which ultrasound cannot provide (Tangedahl, 1979). If it is wished to detect cases of adenomyomatosis, OCG is the investigation of choice (de Lacey et al, 1984).

This regimen for the investigation of non-acute gallbladder disease can be applied easily in any X-ray department. It has been shown to be effective in our hands. Only a small number of patients (12.2%) require two tests and, therefore, it does not involve any significant increase in work-load for the radiology staff. From a single visit by the patient to the X-ray department, the referring clinician will be provided with objective evidence on which to base subsequent management.

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Book reviews

Current Topics in Bioenergetics, Vol. 14. Ed. by C. P. Lee, pp. xv + 192, 1985 (Academic Press, New York), £35.00/$39.50.
ISBN 0-12-152514-7

The interface between biology and physics is particularly strong in the field termed bioenergetics, an all-embracing term for the biology involved in the synthesis and breakdown of adenosine triphosphate (ATP), the "universal energy carrier" of cells. One reason for this is that the biological systems involved in ATP synthesis are particularly suitable for spectroscopic investigations: for example, most of the oxidation-reduction processes of bioenergetics involve molecules either with optical transitions in the visible region of the spectrum (for example, haemoproteins, flavin and pyridine nucleotides) or with well defined electron paramagnetic resonance (EPR) properties, for example, non-haem iron or copper-containing proteins.

Generally speaking, new developments in spectroscopy, used here in its widest sense, are not always applied to biological systems because they are thought to be either "too complicated" to study or "too fragile" for the energies involved. This volume of *Current Topics in Bioenergetics* puts the record straight and describes the application of a variety of spectroscopic procedures, some of which are quite novel, to biological systems. The techniques described are not restricted to bioenergetics, although this is a favoured field for biologists with a strong background in physical chemistry. The chapters are much easier to follow when the reader has some prior, albeit minimal, knowledge of the particular approach. This suggests that the volume will not be the natural first choice for readers seeking an introduction to an entirely new field. However, for those with an interest in particular aspects of biological spectroscopy, this volume gives a useful lead into significant, modern developments. The chapter on EXAFS shows how the precise structures of enzymatic intermediates can be assessed and provides, for the first time, a convincing physical basis for the complete reduction of oxygen to water without the release of partially reduced, toxic intermediates. The chapters on NMR show how nuclei other than ^{1}H, ^{13}C or ^{31}P can be used to study biological processes both in model systems and, in the case of ^{23}Na and ^{39}K, in living cells as well.

In addition, there are useful chapters on the uses of X-ray and neutron diffraction for the study of small molecules embedded in membranes and on the application of optical activity spectroscopy (ORD and CD) to the study of protein conformation.

C. L. BASHFORD

Radiology Today 3. Ed. by M. W. Donner and F. H. W. Heuck, pp. xv + 203, 196 figs, 1985 (Springer-Verlag, Berlin), DM 156 (£45.00 approx.).
ISBN 3-540-13438-7

Keeping up to date is a constant problem in medicine, and radiology seems to develop a never-ending list of new techniques of investigation and treatment. Enthusiasm for particular methods waxes and wanes and it takes much discussion, time and experience to select the right investigation to solve a particular problem with the minimum fuss and the maximum benefit for the patient.

This book is based on the proceedings of a "Multinational Postgraduate Course" held in Salzburg in 1984 and it attempts to guide the reader through the available diagnostic and "interventional" methods of investigating and treating some abdominal and genito-urinary-tract problems. It ends with a disparate and unrelated series of papers on digitisation of images, paramagnetic contrast media and costs and cost-containment in radiology, with some reference to developing countries.

Little of the material presented is new, and some papers are so succinct that their chief value is in providing a list of relevant references. Reichardt's paper on localisation of hormonally active pancreatic tumours is a very useful summary of the current position, as is that by Ferrucci on percutaneous drainage of abdominal abscesses. Igor Laufer's paper on double-contrast gastrointestinal studies will be well known to most radiologists and the illustrations, in the main, come from his book on the subject. There is a thoughtful summary of the current situation in low-osmolality contrast media in urography by Hugh Saxton, while Burhenne discusses percutaneous gallstone extraction and stricture dilatation. Vena-caval filters, lithotripsy, percutaneous stone removal and angiography in gastrointestinal bleeding are also presented. Margulis ends a cryptic one-page paper on "Avoidance of Duplication (of investigations) through Education of Physicians" with a summary of the future directions of MRI. The first direction is artificial intelligence.

All in all a very mixed bag which, pending the arrival of the all-knowing intelligent computer, may be useful if you do not have regular access to the radiological literature.

W. D. JEANS

1986, *The British Journal of Radiology*, *59*, 475–480

MAY 1986

Who has most epidural fat? Information from computed tomography

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ABSTRACT

The amount of epidural fat at the L3 level was assessed in 30 consecutive patients undergoing computed tomography of the lumbar spine. The amount of fat around the theca and nerve roots has been shown to be related to the antero-posterior diameter of the canal, the thecal cross-sectional area and the obesity index. Men had a greater quantity of epidural fat than women, although this difference did not reach statistical significance when allowances were made for the inherent difference in size of vertebral structures between the sexes.

Computed tomography (CT) is now an established method of investigating disorders of the lumbar spine (Williams et al, 1980; Fries et al, 1982; Dixon, 1986). Indeed, in many centres it is regarded as the optimal test and, being non-invasive, it is often used instead of radiculography. In order to maintain the non-invasive nature of the procedure, most centres routinely perform CT without using either intravenous or intrathecal contrast medium. However, the inherent density difference between theca and low-attenuation disc material may not be all that great. The recognition of fragments of herniated disc material, therefore, either in expected or unexpected sites, largely depends on the obliteration or displacement of normal epidural fat by material of soft-tissue density at the relevant site. In patients with copious epidural fat such abnormalities should be readily recognised; however, in patients with little epidural fat, interpretation can be difficult.

Because of obvious differences in the amount of epidural fat present in different patients, it was considered of interest to try to quantify the amount of fat and assess this variation. It might be expected that the amount would be reduced in patients with narrow spinal canals, but is it? Also, does the amount of fat vary with obesity? Is there a difference in the distribution of fat at this site between the sexes, as has been shown elsewhere in the body (Dixon, 1983a)? These and other questions have been addressed in an attempt to identify those patients with the least epidural fat so that the radiologist is forewarned of those patients in whom diagnostic difficulties might be expected to occur.

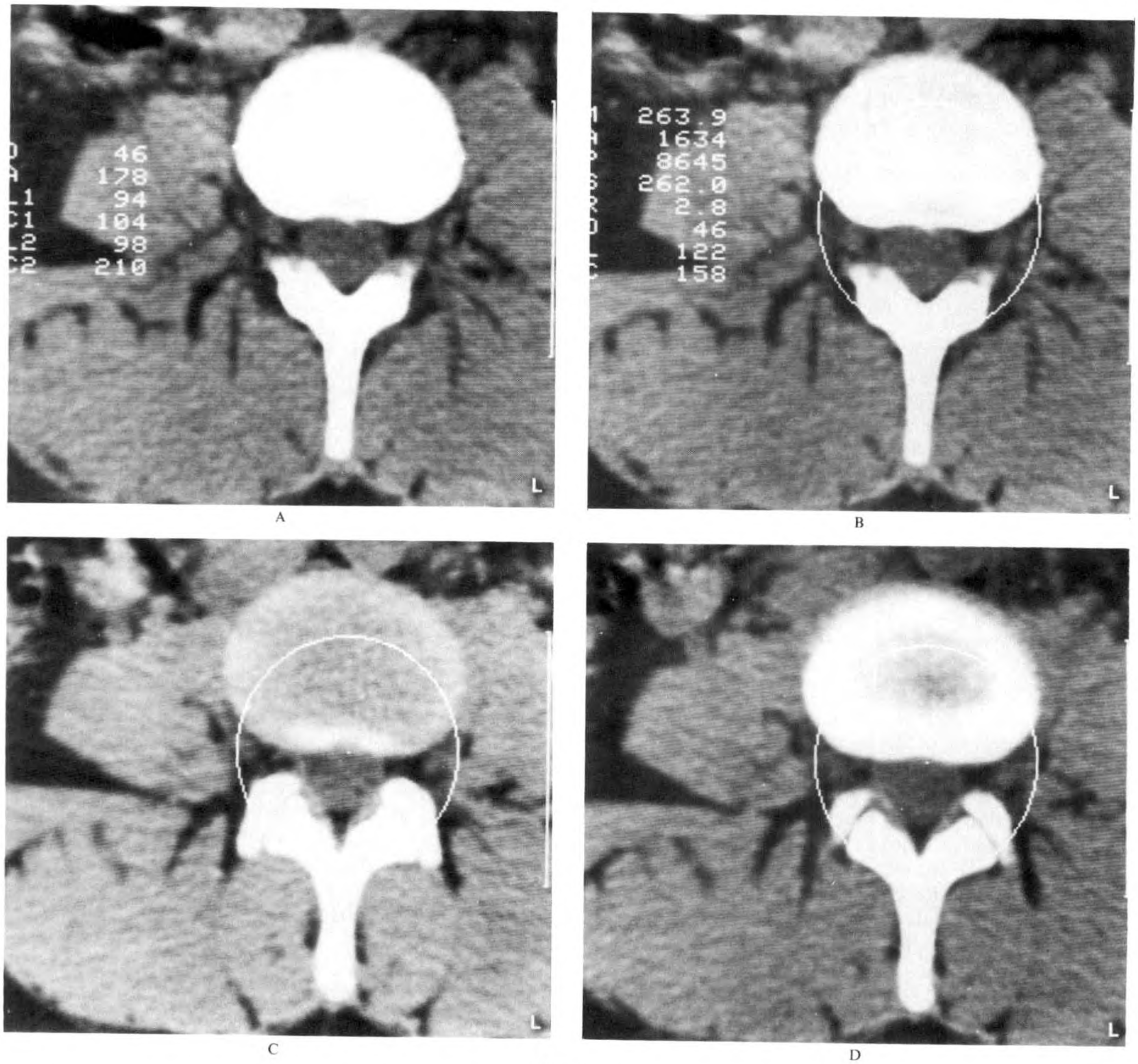
PATIENTS AND METHODS

Thirty consecutive patients referred for CT of the lower lumbar spine form the basis of this study. At the time of the study the patient's age, height and weight were recorded, as well as the minimal waist girth and maximal hip girth as described by Ashwell et al (1982). From these measurements both the obesity index (OI: weight, kg/height^2, m^2) and waist to hip ratio (WHR: waist girth/hip girth) could be derived.

A standard routine for CT of the lumbar spine has been adopted in the body CT unit at Addenbrooke's Hospital (Dixon, 1983b) which is very similar to that established in other centres (Chafetz et al, 1983). This routine involves 4 mm-thick cuts which extend at 5 mm intervals from the pedicles of one vertebra to the pedicles of the next, with intervening cuts obtained as required. The gantry is angled so that cuts are parallel to each disc space in turn. The L3 to S1 segment of the spine is studied. For the purposes of this study, the information obtained at the L3–L4 level was chosen for further analysis. At this level little or no gantry tilt is required and, therefore, this factor was not considered further during the study. The L3–L4 disc is also less often affected by disease than the lower levels; in this study it was essentially normal in all patients (apart from some degenerative changes and minor examples of bulging annulus).

In each patient three sequential images were analysed. The first was approximately 10 mm cranial to the L3–L4 disc space (A). The next (B) was 5 mm above the L3–L4 disc space and the third (C) traversed the L3–L4 disc. Inevitably, the sequence of images started at slightly varying points but by choosing the image most closely traversing the L3–L4 disc (C) and the two adjacent cranial images (B and A), consistency was maintained to less than 3 mm between patients.

On Image A the transverse diameter of the L3 lumbar vertebra was measured (TD) (Fig. 1A). A circular region of interest (ROI), using this diameter, was constructed and placed so that its posterior margin coincided with the posterior borders of the laminae (Fig. 1B). The area of the ROI and the number of pixels included were calculated. Then the number of pixels occupied by material in the fat density range (−150 to −50 HU) was determined by means of histogram mode analysis and so the area of fat within the described region could be calculated. The area of fat within this ROI was similarly assessed for Images B and C, again placing the same circular ROI on the posterior borders of the



A B

C D

Fig. 1.

(A) Typical patient from the series, a 35-year-old female. Image A. Electronic calipers show the transverse diameter of the vertebral body (46 mm). (B) The same image (A) as Fig. 1A. Circular ROI of 46 mm diameter placed so that the posterior margin coincides with the posterior margin of the laminae: 8645 pixels within this region of 1634 mm^2. Within this ROI, 317 pixels were of fat-density, giving an area of 60 mm^2. (C) Image B, 5 mm caudal to Image A. Similar circular ROI. Again, the area of fat within this ROI was calculated (51 mm^2). (D) Image C, 5 mm caudal to Image B, traversing the L3–L4 disc. Position of ROI as shown; this contained 61 mm^2 of fat. These three measurements (A: 60, B: 51 and C: 61) provided an average quantity of fat of 57.3 mm^2, therefore 3.51% of the ROI is occupied by fat. (L + 90, W 512.)

laminae (Figs 1C, D). By using the diameter of the vertebra in Image A, some potential problems of endplate expansion and syndesmophytes on the lower images were avoided. This region of interest included not only all the fat surrounding the theca, but also fat within and adjacent to the neural foramen at the site where lateral disc prolapse is of importance (Williams et al, 1982). By taking an average of the areas of fat from the three images (A, B and C), an average quantity of epidural fat was obtained for each patient. By comparing this average area with the area of the original ROI, the percentage of the ROI occupied by fat was calculated in each patient in order to allow for the variation in vertebral size.

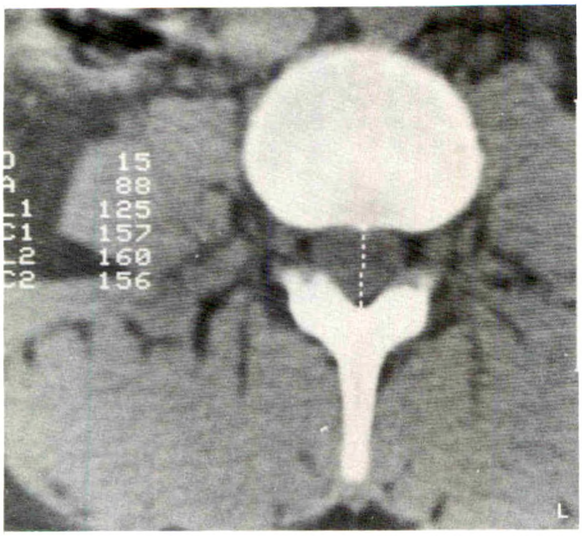


FIG. 2.

The same patient and image as shown in Fig. 1A (Image A) but displayed at L + 100, W 1024. Electronic calipers show the AP diameter (15 mm).

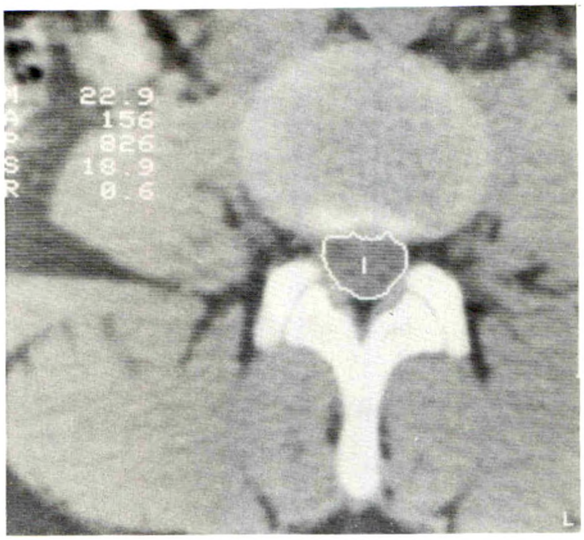


FIG. 3.

The same patient as shown in Fig. 1. Image C, through the L3–L4 disc. Region of interest drawn around thecal sac to evaluate thecal cross-sectional area (156 mm^2). (L + 100, W 1024.)

TABLE I

DETAILS OF 30 PATIENTS

	Mean	SD	Range
Age (years)	42.0	14.1	21–72
AP canal diameter (mm)	14.7	2.3	11–19
Vertebral transverse diameter (TD, mm)	49.0	4.8	42–60
Theca cross-sectional area (mm^2)	158.0	65.2	42–306
Average quantity of epidural fat (mm^2)	54.0	26.7	11.7–137
Percentage of fat within ROI	2.89	1.39	0.69–6.15
Obesity index (OI)	27.8	4.8	17.8–39.5
Waist–hip ratio (WHR)	0.84	0.07	0.68–0.96

The antero-posterior (AP) diameter of the spinal canal was measured on Image A, immediately below the pedicles, where the laminae still fuse in a curved, rather than an angular, fashion (Fig. 2). The cross-sectional area of the thecal space was measured by means of a region of interest drawn around the theca at the L3–L4 level (Image C, Fig. 3). For both of these last measurements a wide window-width (1024 HU) and a suitable level (+100) were used in order to prevent errors caused by the partial volume effect (Koehler et al, 1979).

The average quantity of epidural fat and the percentage of fat present within the region of interest were both correlated with the patient's age, the AP diameter of the canal, the transverse vertebral diameter, the cross-sectional area of the theca at L3–L4, the

TABLE II

CORRELATION MATRIX

		1	2	3	4	5	6	7	8
1	Age	1							
2	AP canal diameter	−0.26	1						
3	Vertebral transverse diameter	−0.20	0.30	1					
4	Theca cross-sectional area	−0.29	0.75‡	0.10	1				
5	Average quantity of fat	−0.20	0.55†	0.34	0.40*	1			
6	Percentage of fat within ROI	−0.22	0.41*	−0.06	0.34	0.88‡	1		
7	Obesity index	−0.34	0.27	0.15	0.08	0.45*	0.49†	1	
8	Waist–hip ratio	−0.02	−0.04	0.57†	−0.19	0.29	0.10	0.17	1

p values: * <0.05, † <0.01, ‡ <0.001.

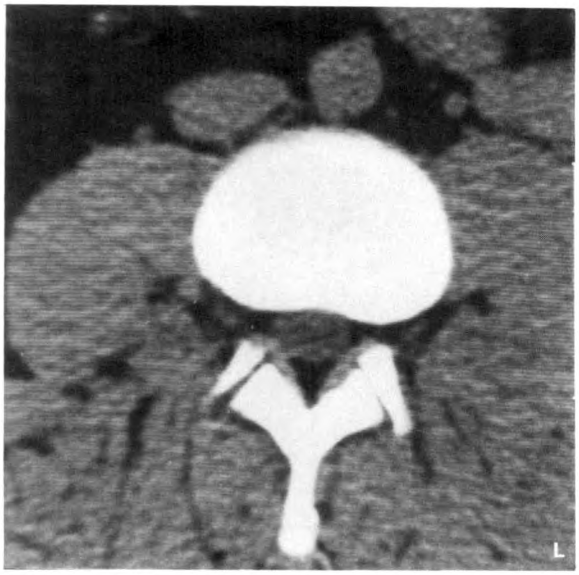


FIG. 4.

Image B from a 25-year-old male patient. This patient had the greatest average quantity of epidural fat found in this series (137 mm^2). The percentage of the ROI occupied by fat was also the highest (6.15%). Normal AP diameter (17 mm). (L+100, W 512.)

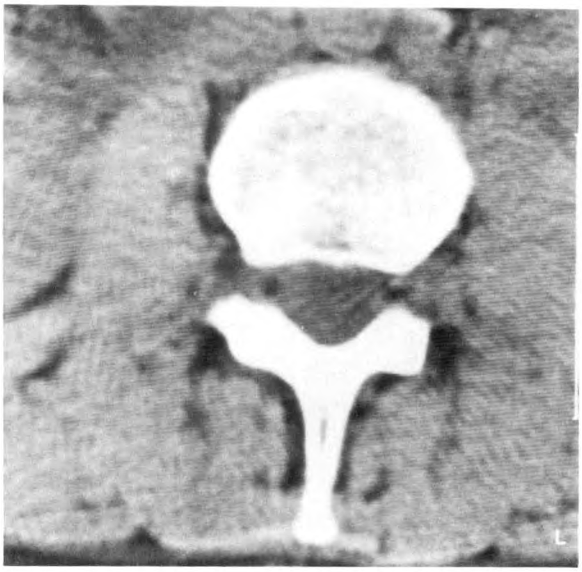


FIG. 5.

Image A from a 51-year-old female patient. This patient had the lowest average quantity of epidural fat (11.7 mm^2). The percentage of the ROI occupied by fat was also low (0.69%). This patient was relatively slender (OI 26.6) and some streak artefacts are present. The AP canal diameter is adequate (15 mm) and the theca quite capacious (cross-sectional area 164 mm^2). (L+90, W 512.)

obesity index and the waist–hip ratio. Statistical testing was by Spearman's rank correlation. These various factors were also compared between men and women using Wilcoxon's rank sum test.

RESULTS

The full details of the 30 patients are shown in Table I. Thirteen patients were male. Table II is a correlation matrix of the various parameters.

Table III shows the differences in the results between men and women. Men have a greater average quantity of epidural fat than women (mean 65.6 mm^2 vs 45.0 mm^2, $p < 0.05$) but their vertebral-body diameters were also larger (mean 52.9 mm vs 46.1 mm, $p < 0.01$).

Illustrated examples are shown in Figs 4–8.

DISCUSSION

In most areas of the body, CT interpretation is easier in patients with moderate obesity than in those who are very lean. Gross obesity, however, is detrimental to image quality; grainy images can occur because of poor signal-to-noise ratio caused by excessive attenuation.

TABLE III

COMPARISON OF EPIDURAL FAT AND OTHER PARAMETERS BETWEEN MEN AND WOMEN

	Men (n = 13)			Women (n = 17)			p
	Mean	Median	SD	Mean	Median	SD	
Age (years)	35.6	28	14.0	46.9	48	12.4	<0.05
AP canal diameter (mm)	15.6	17	2.6	14.1	14	2.6	NS
Vertebral transverse diameter (TD, mm)	52.9	51	3.5	46.1	46	3.4	<0.01
Theca cross-sectional area (mm^2)	164	136	74.7	153	138	59.0	NS
Average quantity of epidural fat (mm^2)	65.6	60.7	28.6	45.0	39.0	22.0	<0.05
Percentage of fat within ROI	3.02	2.75	1.29	2.78	2.04	1.49	NS
Obesity index	27.5	29.4	4.9	28.3	26.8	4.9	NS
Waist–hip ratio	0.88	0.90	0.05	0.80	0.76	0.06	<0.01

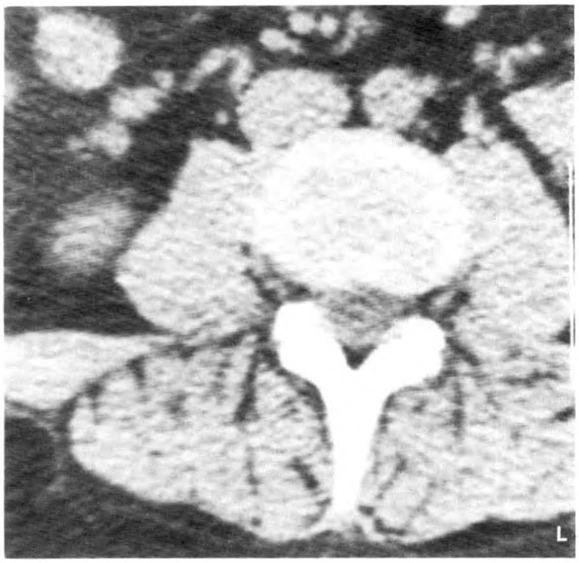


FIG. 6.

Image C from a 23-year-old female patient. This was the fattest patient in this series (OI 39.5). Only a moderate average quantity of epidural fat (75 mm^2) was present. Note the rather grainy image. (L + 90, W 512.)

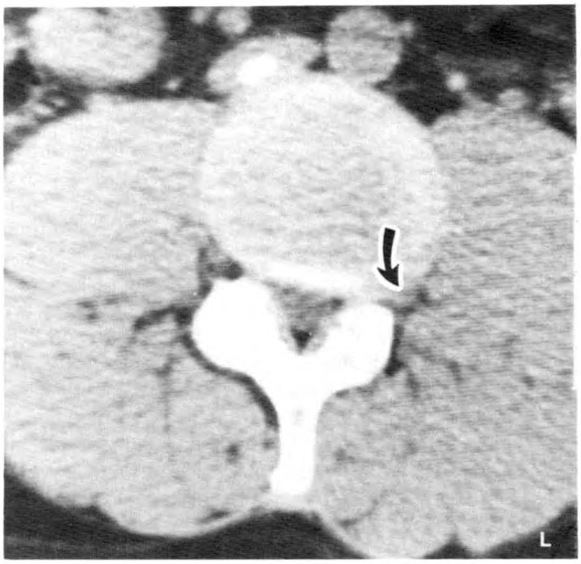


FIG. 8.

Image C from a 48-year-old male patient with a reduced AP diameter (11 mm), reduced thecal cross-sectional area (78 mm^2) and little epidural fat (average = 47 mm^2). The paucity of fat makes it hard to identify the left L3 nerve root (arrow), separate from the postero-lateral margin of the L3/L4 disc. Considerable muscle hypertrophy accentuates the problem. (L + 90, W 512.)

This can also be a problem when examining the lumbar spine in the very obese (Fig. 6). In general, however, a moderate quantity of subcutaneous fat facilitates the examination as the spine seems to be more buttressed, thereby causing artefacts to be less apparent than in the very thin (Fig. 5). Against this background, the fact that the percentage of epidural fat within the ROI did relate to the obesity index ($r = 0.49$, $p < 0.01$) is of interest.

It is not very surprising that the amount of epidural fat was found to correlate with the AP diameter of the canal, the size of the vertebral body and the cross-sectional area of the thecal space, as all are parameters of the likely overall space in the epidural region. Indeed, lack of epidural fat is a recognised indicator of spinal stenosis (Dorwart et al, 1983). It might be expected that the average quantity of fat would start to diminish in those patients with very capacious thecal sacs filling the whole canal and thereby displacing fat. Although this did occur in a few patients (*e.g.* Fig. 5), the five patients with very large thecal cross-sectional areas (over 200 mm^2) had quite adequate average quantities of fat (range 39–78, mean 65 mm^2).

Although men had more fat around the theca and nerve roots than women (65.6 mm^2 vs 45.0 mm^2, $p < 0.05$), their vertebral-body diameters were larger (52.9 mm vs 46.1 mm, $p < 0.01$). This latter fact contributed to the fact that the difference in the amount of epidural fat between men and women was slight when it was expressed as a percentage of the ROI examined (3.02 vs 2.78, NS). Nevertheless, the more fat there is around the theca and nerve roots the better as far as interpretation is concerned. Thus, it would seem

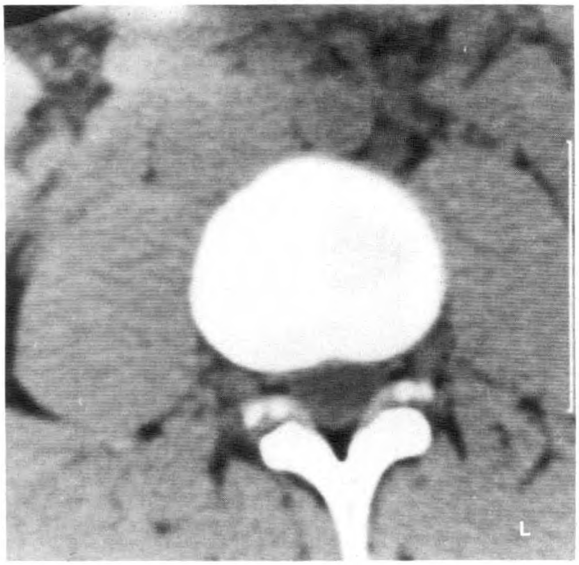


FIG. 7.

Image B from a 21-year-old male patient. This was the thinnest patient in this series (OI 17.8). There is adequate epidural fat (average = 48 mm^2), allowing good detail of nerve roots and epidural veins. (L + 90, W 512.)

that the relative difference in the amount of epidural fat between men and women lies somewhere between that found within the abdomen (men : women, *c*. 2 : 1) and that present in subcutaneous tissues (men : women, *c*. 1 : 1) (Dixon, 1983a). Further evidence that the distribution of epidural fat does not follow intra-abdominal fat distribution is provided by the fact that the amount of epidural fat was not related to the waist-hip ratio which is known to relate to intra-abdominal fat stores (Ashwell et al, 1985).

So the plumper patient with a wide AP canal diameter has the most fat around the theca and nerve roots and, thus, should provide the best images on CT. Conversely, the thin patient with a narrow AP canal diameter has the least fat around the theca and nerve roots and, therefore, fine detail on the CT images may be lacking. In this series, women had less epidural fat than men although the difference is only statistically significant when expressed in absolute areas. It is worth remembering these factors before making an important decision on images which are less than ideal. Similar relative limitations are likely to occur with magnetic resonance imaging.

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Cholesterol granuloma of the facial skeleton

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ABSTRACT

The radiological features of 24 patients with cholesterol granuloma affecting the facial skeleton are described. They occurred at two sites. (a) in the maxillary antrum (nine patients) and (b) in the frontal bone, affecting the supero-lateral orbital wall and adjacent soft tissues (15 patients). The radiographic features of the antral cholesterol granuloma were of two types. a variety in which the changes were entirely non-specific and could not be differentiated from inflammatory or allergic sinus disease, and a more characteristic appearance of a cyst-like lesion within the sinus cavity accompanied by expansion of the bony walls of the antrum involved. The radiographic changes encountered in the cholesterol granuloma of the frontal bone were more specific and were best demonstrated by plain radiography. The typical radiological picture was that of a clear-cut area of osteolysis in the lateral part of the supraorbital ridge and frontal bone, characteristically extending into the zygomatic process as far as the fronto-malar suture This change is regarded as being diagnostic of a cholesterol granuloma in this situation.

In the head and neck, cholesterol granuloma is most frequently found in the mastoid antrum and middle ear following haemorrhage and is not an uncommon accompaniment of middle-ear disease. It has also been described in other parts of the skull, including the maxillary antrum (Graham & Michaels, 1978; Hellquist et al, 1984) and in the frontal bone forming the supero-lateral boundary of the orbit (Nichols, 1956; Wright, 1970). The condition is totally unrelated to cholesteatoma; the latter is a post-inflammatory response with the formation of squamous epithelium and keratin, while cholesterol granuloma is essentially a granulomatous change provoked by the formation of cholesterol crystals. The histology is the same whether the lesion is found in the middle ear, maxilla or frontal bone.

The purpose of this paper is to present the radiological features of 24 patients with histologically verified cholesterol granuloma involving the facial skeleton at two sites: (a) in the maxillary antrum and (b) in the frontal bone, affecting the supero-lateral orbital wall and adjacent zygomatic process.

CASE MATERIAL

Maxillary antrum

There were nine patients in this group (seven male, two female) with an age range of 27–56 years and an average age of 38.4 years. The commonest presenting symptoms were nasal obstruction (three patients), rhinorrhea (two patients) and facial pain (two patients), and two patients initially complained of otalgia. The duration of symptoms ranged from 3 months to 10 years with an average duration of 2.75 years. In addition, there was a past medical history of sinus disease in five patients, four of whom had undergone surgery previously.

Radiological findings. (1) Five patients showed non-specific changes on plain radiographs, with polypoid mucosal thickening and no bony changes apparent.

(2) Four patients showed a cyst-like expansion within the antral cavity associated with destruction of the antral walls. These changes were best demonstrated by computed tomography (CT) (Figs 1, 2) or hypocycloidal tomography (Fig 3). In two patients the lateral antral wall was shown to be eroded on plain radiographs, raising the possibility of malignant disease.

(3) One patient showed irregularity and sclerosis of the bony walls of the affected antrum, together with expansion of part of the antral cavity (Fig. 1). The sclerosis could, however, be attributed to previous surgery (Caldwell-Luc procedure) and there was no evidence to suggest that it was due to cholesterol granuloma.

In summary, the radiological features in those antra with proven cholesterol granuloma were of two types: one variety in which the changes were entirely non-specific and could not be differentiated from inflammatory or allergic sinus disease, and a more characteristic appearance of a cyst-like expansion within the sinus cavity accompanied by expansion of the bony walls of the antrum involved

Frontal bone

There were 15 patients in this group (14 male, one female) with an age range of 30–58 years and an average age of 44.13 years. By far the commonest presentation was the presence of proptosis (10 patients), noted either by the patient or by the clinician. In some patients this was accompanied by a downward displacement of the globe (four patients). Five patients also complained of diplopia. Other signs and symptoms included ptosis (four patients) and visible swelling (three patients): pain was a feature in three patients and one patient initially complained of epiphora and poor vision. The duration of the symptoms ranged from 1 month to 3 years with an average duration of 1.05 years.

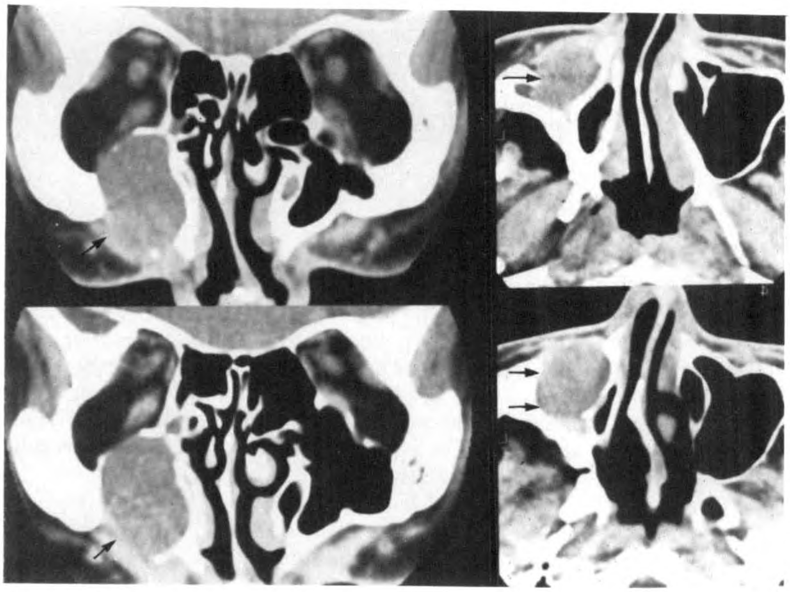


FIG. 1.

Coronal and axial CT sections showing an expanded loculus of the maxillary antrum due to a cholesterol granuloma (arrows). The patient had undergone a Caldwell-Luc procedure on the affected antrum many years previously.

Radiological features. (1) Fourteen patients showed an osteolytic defect in the diploë of the frontal bone and supero-temporal orbital margin. Extension into the zygomatic process was present in 10 of the 14 patients and extended to the fronto-malar suture in seven. Figures 4 and 5 show the margins of the defect were characteristic in that there was always a clear-cut edge at the point of demarcation with the normal bone, but the edge was never sclerotic.

(2) One patient showed a unique appearance in that the lesion was essentially located in the lateral part of the soft tissues of the orbit and had caused a local erosion of the bone of the lateral orbital margin.

(3) Computed tomography was performed in eight patients. All showed an osteolytic defect, as demonstrated by plain radiography, associated with a soft-tissue mass extending into the adjacent orbit (Fig. 6). There were no characteristic features in the attenuation values of the soft-tissue mass which might differentiate this lesion from other space-occupying lesions in the orbit.

In summary, over 93% of patients showed a

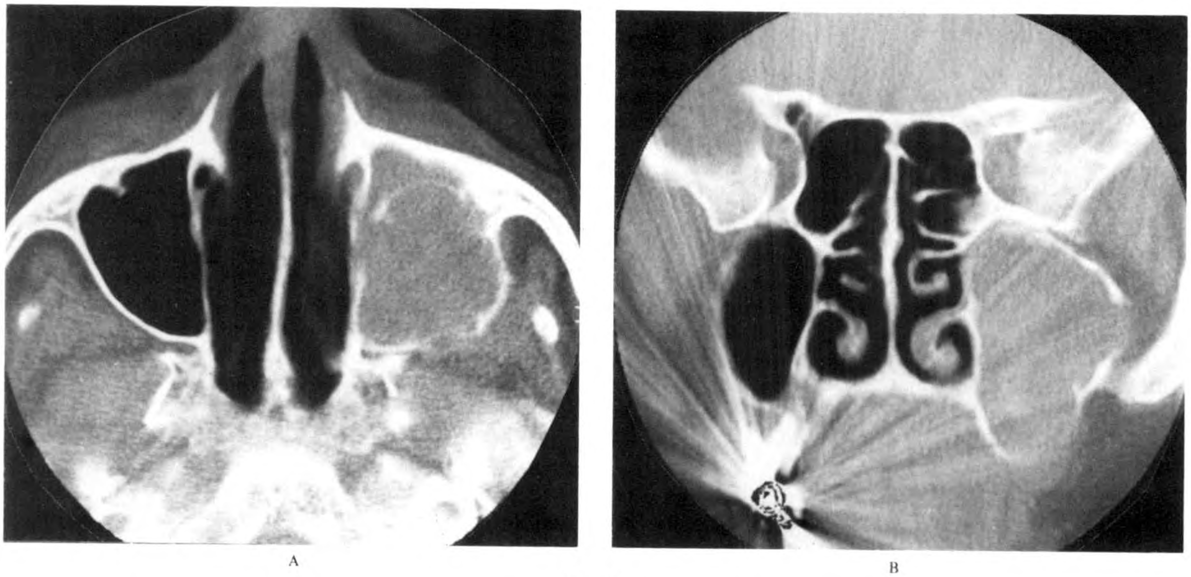


FIG. 2.

Antral cholesterol granuloma. (A) Axial CT section showing expanded maxillary antrum and a cyst-like expansion within the antral cavity. (B) Coronal section showing gross expansion of the maxillary antrum.

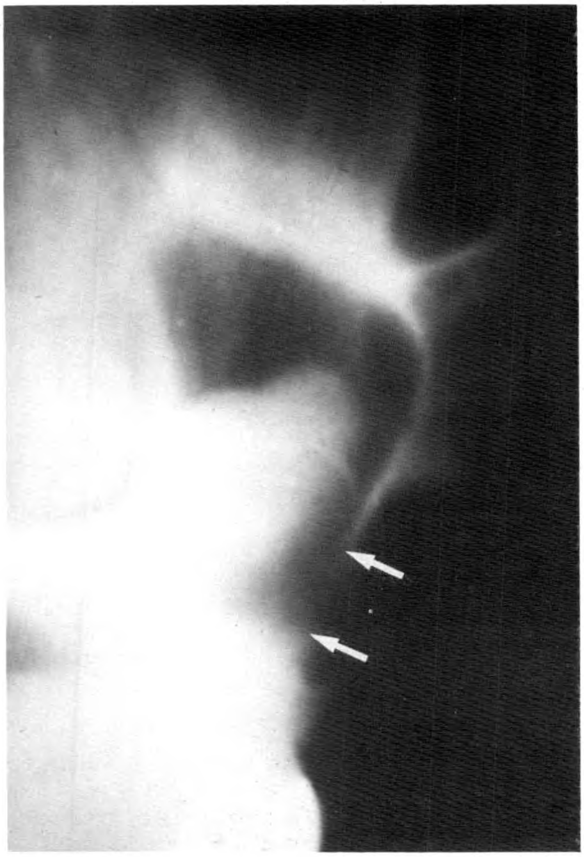


Fig. 3.

Cholesterol granuloma of the maxillary antrum. Hypocycloidal tomogram showing a polypoid soft-tissue mass and local erosion of the lateral margin of the sinus (arrows).

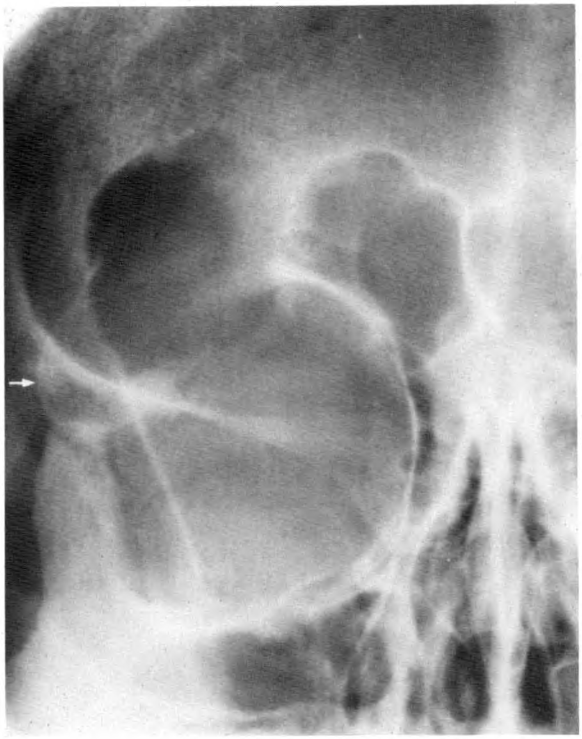


Fig. 4.

Characteristic plain radiographic appearance of a cholesterol granuloma affecting the orbit and frontal bone. There is a sharply demarcated area of osteolysis with extension into the diploë of the zygomatic process (arrow) down to the fronto-malar suture.

diagnostic appearance consisting of a clear-cut, osteolytic defect in the frontal bone and superotemporal orbital margin. In two thirds there was extension within the diploë of the zygomatic process of the frontal bone, frequently reaching as far as the fronto-malar suture. These radiological features were remarkably uniform and were better demonstrated on plain radiographs than by CT scan.

Discussion

The typical histological features in the 24 patients described showed, in all cases, granulomatous tissue with typical cholesterol clefts (Fig. 7) surrounded by foreign-body giant cells and associated with evidence of haemorrhage with both intact and degenerated red cells and the presence of haemosiderin. Electron microscopic studies of cholesterol granuloma related to the middle ear have been carried out by Friedmann and Graham (1979). These have shown that the giant cells contain cholesterol needles covered by a lipid-like, amorphous material. Larger cholesterol needles are found scattered in the associated granulation tissue. The needles are often surrounded by plasma cells, lymphocytes, histiocytes and red blood cells. Graham and Michaels (1978), in reviewing a series of five antral cholesterol granulomas, postulated that when blood stagnates in a closed space, cholesterol comes out of solution as crystals, the latter provoking the granulomatous process, the key factor in the aetiology being the presence of a closed cavity containing exudate and blood. This would imply that poor drainage from the site of haemorrhage and stagnation is an important aetiological factor, because cholesterol is relatively insoluble and needs time to become dissociated from the lipoprotein complex and be precipitated as crystals (Hellquist et al, 1984). The essential condition for cholesterol granuloma formation would be fulfilled in a maxillary antrum with blocked ostium, and similar conditions would also be realised in the case of a haemorrhage into the diploë of the frontal bone. In orbital cholesterol granuloma, Ramsey et al (1948) also believed that the lesion was initiated by haemorrhage with deposition of blood, release of blood pigments and the formation of cholesterol crystals, producing a foreign-body granuloma. These authors also thought

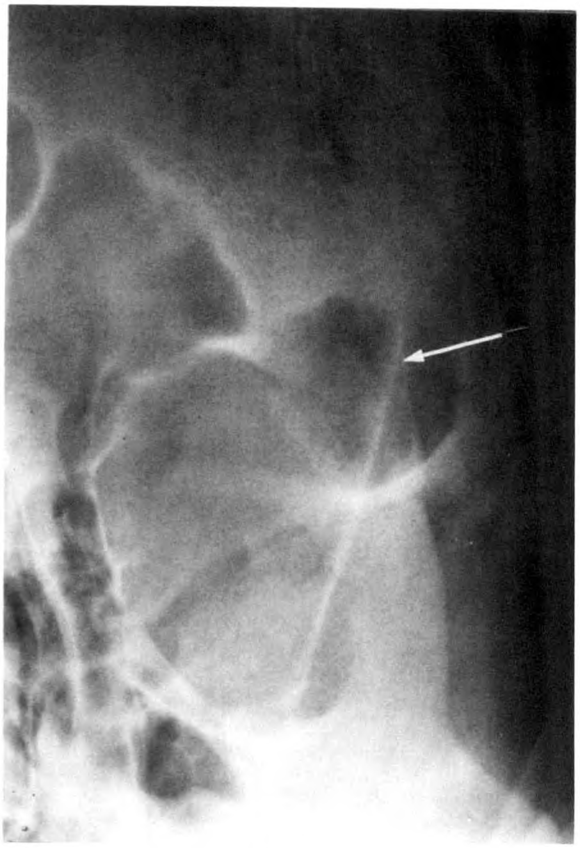


Fig. 5.

Small area of osteolysis due to a cholesterol granuloma (arrow). As in Fig. 4, there is extension to the fronto-malar suture.

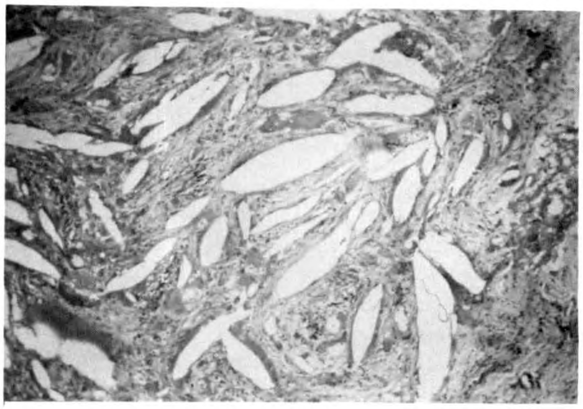


Fig. 7.

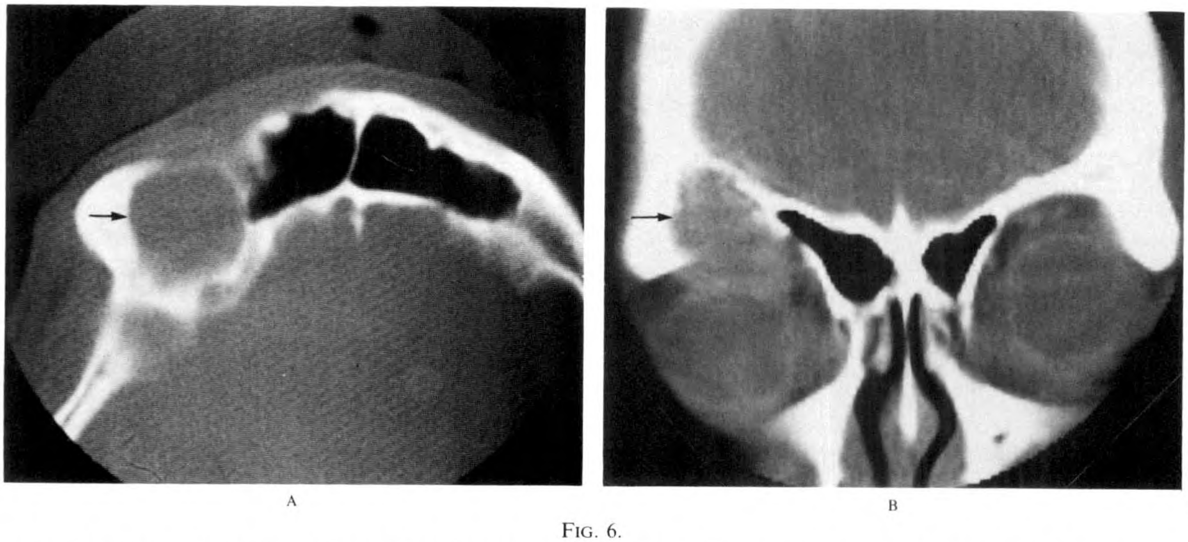
Histological appearance of cholesterol granuloma showing typical cholesterol clefts.

that trauma was the cause of the initial haemorrhage in the frontal bone. However, there was little evidence of trauma in the patients described in this series. Only two patients gave a history of trauma and in both instances this was minor and not related directly to the site of the lesion or to the onset of symptoms.

Differential diagnosis

Although the age and sex incidence is similar in cholesterol granuloma whether the lesion is located in the maxillary antrum or orbit, the presenting symptomatology and radiological features differ according to the site.

Maxillary antrum. The radiological differential diagnosis of antral cholesterol granuloma includes a mucocoele of the antrum and such conditions as mucus



A

B

Fig. 6.

Axial (A) and coronal (B) CT sections showing the soft-tissue mass of the cholesterol granuloma and osteolytic defect (arrows).

retention cysts and non-secreting cysts arising in the sinus. The latter, it should be noted, usually has a high cholesterol content in the cyst fluid. In this series there are two distinct radiological groups, one needing differentiation from a mucocoele in that there was an expansion of the antrum and a second variety with only polypoid thickening of the lining membrane. The latter type is radiologically indistinguishable from a small polyp or cyst. With regard to the relationship of cholesterol granuloma to mucocoele formation, it could be envisaged that when the ostium is blocked, if haemorrhage into the sinus ensues, suitable conditions exist for the development of cholesterol granuloma, while in the absence of haemorrhage a mucocoele may develop. Support for this hypothesis was given in the case illustrated in Fig. 1 when, at surgery, the maxillary antrum was found to be partitioned, there being evidence of mucus retention in one part and a cholesterol granuloma in the other, both conditions being associated with a blocked ostium and inadequate drainage from the sinus. With regard to the five cases with cholesterol granuloma with a non-expanded antrum, it is tempting to regard them as a variety of non-secreting cyst. Certainly, the two conditions could not be distinguished on radiological grounds. However, histologically, these lesions were described as cholesterol granulomas.

Frontal bone. In the frontal bone cholesterol granuloma is characterised by a clear-cut bone defect on the temporal side of the orbital roof, with the formation of a soft-tissue mass below the supraorbital ridge (Fig. 6). The main differential diagnosis is, therefore, from other conditions which cause local bone erosion in this part of the orbit, such as lacrimal gland tumours and dermoids. Lacrimal gland tumours seldom cause a clear-cut defect that could be confused with cholesterol granuloma. Usually, they produce local pressure erosion when benign or simply cause a generalised enlargement of the lacrimal fossa. Malignant lacrimal-gland tumours may produce similar features or invade the bone directly, in which case they cause either an ill-defined osteolysis or, in some patients, bone sclerosis. Dermoids are more difficult to differentiate, but there are three features which help to distinguish them from cholesterol granuloma.

(1) The osteolytic defect of a dermoid usually has a well defined, sclerotic border.
(2) Dermoids do not extend in the diploë of the zygomatic process of the frontal bone to the fronto-malar suture.
(3) Approximately two-thirds of dermoids will show areas of negative attenuation on CT scan due to the presence of oil or fat. This has not been observed in cholesterol granuloma.

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Book reviews

Computed Tomography of CNS Disease A Teaching File. By D. H. Yock Jr, pp. xiv+258+references, 1985 (Year Book Medical Publishers, Chicago), £43.00.
ISBN 0-8151-9814-0

This book is a collection of computed tomographic scans of the head, orbits and spine organised into 13 chapters covering the major pathological diagnoses found in these areas Each scan is a "case" and a one- or two-line history is given before the scan, which is followed by a short discussion on the appearances. Four hundred and thirty-seven cases are presented and there is a table of illustrated differential diagnoses at the start of the book which refers to pages on which cases with similar appearances, but with different aetiologies, are discussed The book is complete with an adequate list of references at the end of each chapter and a good index.

The cases have been selected to demonstrate both the usual and the unusual appearances found, and the changing pattern of disease with time is also well illustrated. This is particularly a feature of cerebral infarction, where scans done too soon after the event may show little or no abnormality The discussion of each case is to the point and the cumulative effect of these short discussions is to impart a considerable amount of easily digested information over the large number of cases demonstrated.

Radiologists enjoy this format, geared as it is to the visual display of disease and with the text kept to the minimum necessary to elucidate the images. The pictures are of excellent quality and the layout of the book is pleasing and easy to follow. The book will be a welcome and frequently consulted addition to the shelves of the increasing numbers of departments that have no neuroradiologists but are concerned with the reporting of CT scans of the head.

W D. JEANS

An Introduction to Emission Computed Tomography. IPSM Report No 44. Ed by E. D. Williams, pp ix+65, 1985 (The Institute of Physical Sciences in Medicine, London), £9.50.
ISBN 0-904181-00-6

This recent publication from the IPSM was produced by the Radionuclide Topic Group of the HPA. It is a short introductory report for anyone associated with the clinical application of emission tomography. The text covers both single-photon and positron emission tomography (SPECT and PET) but concentrates on the use of the rotating gamma camera for SPECT, since this is more generally available.

The book essentially starts with the basic theory of tomographic reconstruction techniques and includes a good description of how filtering can remove image noise. The chapter on the rotating gamma camera then explains how this theory is applied in practice and includes an important section on quality control. The attenuation problem is treated well and illustrates the difficulty in obtaining quantitative information from SPECT Other SPECT techniques are reviewed, including a single-slice system which has better sensitivity and resolution compared with those of the rotating gamma camera. The chapter on PET is short, since few hospitals have access to this facility as yet, but it is made clear that the attenuation correction is easy and quantification becomes possible with PET The last three chapters briefly consider image display, clinical applications and commercial systems. The bibliography and references are essential for this introductory text and will be invaluable to those readers who wish to acquire a deeper knowledge of particular aspects of this subject.

Parts of this book may be too complex for the radiographer or radiologist, yet too simple for the physicist. However, I recommend that all departments of radiology and nuclear medicine should purchase this book Anyone already working or starting to work in emission tomography should consult it

M A. FLOWER

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A prospective study of mammographic parenchymal patterns and risk of breast cancer

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ABSTRACT

Breast parenchymal patterns have been assessed by the method of Wolfe in a prospective study in Guernsey. Women with P2 or DY grades had approximately four times the risk of developing breast cancer compared with those with N1 or P1 grades. Age, weight, parity and age at birth of first child are all related to the distribution of mammographic patterns. The combination of these variables with Wolfe grades may identify subsets of the population at very high risk.

Wolfe (1976, 1977) claimed that mammographic parenchymal patterns could be used to identify women with a high risk of developing breast cancer. While the majority of subsequent reports have confirmed his results, the absolute risk to women whose mammograms show ductal prominence (P2) or increased parenchymal density (DY) has been found to be much smaller than originally described and, in a few instances, no association between mammographic patterns and risk has been found (Boyd et al, 1984). It has also become clear that variables such as age, weight, age at birth of first child and parity are highly related to the proportion of high-risk mammograms found in a population and that these must be taken into account in assessing risk (Gravelle et al, 1980; Brisson et al, 1982; De Waard et al, 1984).

We have been conducting a series of prospective studies in a normal population to see whether women who subsequently develop breast cancer could be identified by antecedent abnormalities in their endocrine function (Bulbrook et al, 1971; Farewell, 1977). In addition, endocrine status has been assessed in various high-risk or low-risk groups (Bulbrook et al, 1978; Wang et al, 1979; Moore et al, 1983; Walsh et al, 1984). If mammographic patterns also identified women at various risk levels, the possibility of carrying out endocrine studies was attractive. The question could be asked whether the Wolfe grades were associated with particular endocrine profiles and the relationship between breast structure and endocrine function could be explored.

As a preliminary step in this investigation it was obviously necessary to confirm that mammographic patterns correlated with risk in our own population and to re-examine the influence of age, reproductive history and weight.

METHODS

Between 1977 and 1984, 4044 normal women living in the Island of Guernsey volunteered to provide a 24 h urine specimen and a 50 ml blood sample. The age distribution of these women is shown in Table I.

The trial was designed to include women aged 35 years or more, but 60 women aged 30–34 years were accepted in error. Their results are included with those of subjects tabulated as being less than 45 years of age.

The volunteers were screened by mammography and clinical examination, usually within 4 weeks of giving the blood specimen. The mammographic technique and the classification of the films by Wolfe's criteria were exactly as described by Gravelle et al (1980). Repeated blind readings of coded mammograms showed a reproducibility of classification of over 90%. Of the 4046 mammograms, 3384 were read by both radiologists. The first radiologist found 33.4% of the population were in the N1 or P1 categories; the second found 32.9%. The proportion of women with P2 or DY grades who subsequently developed breast cancer was 87.5% and 91.7%, respectively.

A diagnosis of breast cancer was made in 31 women, confirmed histologically at biopsy. Of these cancers, 10 were discovered at screening and 21 were interval cases diagnosed at a median time of 35 months after screening (range 6–66 months). The 31 women are defined as "pre-cancer cases" in that they claimed, or were found

TABLE I

AGE DISTRIBUTION OF THE SCREENED POPULATION

Age (years)	No. (%) of women
<35	60 (1.5)
35–44	1950 (48.2)
45–54	1120 (27.7)
55–64	647 (16.0)
65–74	251 (6.2)
>75	16 (0.4)
Total	4044

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§Author for offprints.

to have, no breast symptoms when they entered the trial.

The N1 and P1 grades have been designated "low-risk grades" and P2 and DY as "high-risk grades". Statistical tests were carried out using this dichotomy.

The significance of the distributions of the pre-cancer cases and controls among the Wolfe grades was tested using Fisher's exact test and one-tailed p values are given. In addition, odds ratios (ORs) with 95% limits have been calculated but, in instances where no pre-cancer cases are found in a particular category, only the lower bound has been given.

RESULTS

Total population

The distribution of the N1, P1, P2 and DY grades in the total population and in the pre-cancer cases is shown in Table II.

The difference between the gradings by the two radiologists is trivial (high-risk mammograms, 65% and 66%; pre-cancer cases with P2 and DY grades, 88% and 92%). In the following analyses, only the readings by the first radiologist (R1) have been used, since his gradings encompassed more of the pre-cancer cases.

The cases have a significantly higher proportion of high-risk grades than the controls (88% vs 65%; $p = 0.004$), controls being defined as individuals in the study population who did not develop cancer. The risk associated with the P2 and DY grades is approximately four times that of the N1 and P1 mammograms.

Age

The distribution of mammographic grades in pre-cancer cases and controls, stratified by age is shown in Table III. In the three age ranges examined (<45, 45–50, >50 years) the pre-cancer cases have a higher proportion of high-risk mammograms than the controls. The number of cases is too small for any degree of certainty but the results suggest that the association between the Wolfe grades and risk is strongest in women over the age of 50 years (OR 6.6, compared with approximately 2 for younger women).

If the distribution of the parenchymal patterns in all women aged 45 years or more is examined, then the excess proportion of pre-cancer cases with P2 and DY grades is highly significant (low-risk, 2/792 vs 19/1221, $p = 0.0025$).

Weight

As in a previous survey (Gravelle et al, 1982) the proportion of high-risk grades in the normal population falls with increasing weight, almost entirely due to a decrease in the DY category. There is a trend for the pre-cancer cases to be concentrated in the P2 and DY grades in women weighing <60 kg and 60–66 kg, but the most marked effect is seen in the heaviest women (≥67 kg) (Table IV). The ORs from the lightest to the heaviest groups are 1.2, 3.3 and 11.4 for the P2 and DY grades.

When the results were further stratified by menopausal status, the trends described above were found for both pre- and post-menopausal women (data not shown).

Parity

The proportion of low-risk parenchymal patterns increases with increasing parity (Gravelle et al, 1980). Results in the present series are shown in Table V, where the same trend is apparent. Nulliparous women had 27% of low-risk grades, para 1–2 had 32.5% and para ≥3, 41.8%.

TABLE II

DISTRIBUTION OF MAMMOGRAPHIC GRADES IN PRE-CANCER CASES AND CONTROLS

		Wolfe grade				OR
		N1	P1	P2	DY	
Controls						
($n = 4013$)	R1	381 (10%)	1030 (26%)	1994 (50%)	608 (15%)	—
($n = 3884$)	R2	587 (15%)	734 (19%)	1926 (50%)	637 (16%)	—
Pre-cancer cases						
($n = 31$)	R1	1 (3%)	3 (10%)	20 (65%)	7 (23%)	3.7 (1.3–14.4)
($n = 24$)	R2	0	2 (8%)	19 (79%)	3 (13%)	5.7 (1.4–49.8)

R1 and R2 refer to independent gradings by two radiologists They differ from those described in the methods section where only mammograms measured by both radiologists have been taken into account

Odds ratio is

$$\frac{\text{No. of cancers in P2 and DY}}{\text{non-cancers in P2 and DY}} - \frac{\text{No. of cancers in N1 and P1}}{\text{non-cancers in N1 and P1}}$$

N1 + P1 vs P2 + DY for R1 : $p = 0.0041$,
N1 + P1 vs P2 + DY for R2 : $p = 0.0036$
(Fisher's exact test).

TABLE III

MAMMOGRAPHIC GRADES AND AGE

Age (years)	Low-risk grades		High-risk grades		OR
	N1	P1	P2	DY	
<45					
Controls ($n = 2000$)	249 (13%)	370 (19%)	1032 (52%)	349 (17%)	
Pre-cancer cases ($n = 10$)	1 (10%)	1 (10%)	5 (50%)	3 (30%)	1.8 (0.4–17.4)
45–50					
Controls ($n = 720$)	32 (4%)	157 (22%)	391 (54%)	140 (19%)	
Pre-cancer cases ($n = 4$)	0	0	2	2	(0.2—)
>50					
Controls ($n = 1293$)	100 (8%)	503 (39%)	571 (44%)	119 (9%)	
Pre-cancer cases ($n = 17$)	0	2 (12%)	13 (76%)	2 (12%)	6 6 (1.5–59.2)

N1 + P1 vs P2 + DY at age >50 years, $p = 0.0025$,
N1 + P1 vs P2 + DY at all ages >45 years, $p = 0.0025$
(Fisher's exact test).

Some 40% of the pre-cancer cases were nulliparous, compared with 13% of the Guernsey controls, a difference that is highly significant ($\chi^2 = 15.0$, $p < 0.001$). The pre-cancer cases occur predominantly in the P2 and DY grades for all three parity categories shown in Table V, but the association between mammographic grade and risk appears to be weakest for women with one or two children.

When menopausal status was taken into account, the association between the high-risk grades and parity appeared to be stronger for post- than for pre-menopausal women (data not shown).

Age at birth of first child

A weak association between parenchymal grades and age at first child had been previously demonstrated (Gravelle et al, 1980). Women with an early age at first child had an increased proportion of low-risk grades, but only in post-menopausal women.

This trend is barely apparent in the present series (Table VI), but it should be noted that nulliparous women have not been aggregated with women with a late first child, as is the usual practice.

In women with a first birth before age 24 years, the pre-cancer cases ($n = 10$) all have P2 or DY grades. In

TABLE IV

MAMMOGRAPHIC GRADES AND WEIGHT*

Weight (kg)	Wolfe grade				OR
	N1	P1	P2	DY	
<60					
Controls ($n = 1352$)	100 (8%)	276 (20%)	666 (49%)	310 (23%)	
Pre-cancer cases ($n = 8$)	1 (13%)	1 (13%)	2 (25%)	4 (50%)	1.2 (0.2–11 8)
60–66					
Controls ($n = 1281$)	115 (9%)	299 (23%)	659 (51%)	208 (16%)	
Pre-cancer cases ($n = 8$)	0	1 (13%)	6 (75%)	1 (13%)	3.4 (0.4–151)
≥67					
Controls ($n = 1379$)	166 (12%)	454 (33%)	669 (49%)	90 (7%)	
Pre-cancer cases ($n = 15$)	0	1 (7%)	12 (80%)	2 (13%)	11.4 (1.7–484)

Weight >67 kg: N1 + P1 vs P2 + DY, $p = 0.0017$ (Fisher's exact test).
* Unknown for one control.

TABLE V

MAMMOGRAPHIC GRADES AND PARITY

Parity	Wolfe grade				OR
	N1	P1	P2	DY	
Nulliparous					
Controls ($n = 532$)	31 (6%)	115 (22%)	278 (52%)	108 (20%)	4.2 (0.6–180)
Pre-cancer cases ($n = 12$)	0	1 (8%)	7 (58%)	4 (33%)	
Para 1–2					
Controls ($n = 2043$)	180 (9%)	483 (24%)	1055 (52%)	325 (16%)	1.3 (0.3–7.5)
Pre-cancer cases ($n = 11$)	1 (9%)	2 (18%)	7 (64%)	1 (9%)	
Para ⩾3					
Controls ($n = 1438$)	170 (12%)	432 (30%)	661 (46%)	175 (12%)	
Pre-cancer cases ($n = 8$)	0	0	6 (75%)	2 (25%)	(1.2—)

Para >3, N1+P1 vs P2+DY, $p = 0.013$.

those with a first child at age 24 years or more, there appears to be no association between Wolfe grades and risk.

The data were re-calculated for pre- and post-menopausal women separately. The trends described above occur mainly in the post-menopausal group, but the numbers are small and the data are not shown.

DISCUSSION

In the population of normal women in Guernsey that we have studied, P2 and DY breast parenchymal patterns are associated with a four-fold increase in risk of breast cancer relative to that of women with N1 or P1 grades. When the mammographic pattern results are stratified using age, weight, parity and age at birth of first child, the pre-cancer cases tend to occur predominantly in the P2 or DY grades in each stratum. There may be some particularly high-risk combinations, such as women over 50 years (OR = 6.6), women weighing more than 66 kg (OR = 11.4) and women with a first child before age 24 years (no OR calculation possible), but more data would be required to prove this association.

It is difficult to compare the distribution of mammographic parenchymal patterns found in the present study with that reported by others. The proportion of low-risk mammograms given in the literature averages about 55% and in one large population study (which admittedly contained many women over the age of 70 years) no less than 84% of the women had N1 or P1 grades (Tabar & Dean, 1982). We found only 35% of our volunteers were in those categories. Possible explanations for this variability have been reviewed by Boyd et al (1984) and include the

TABLE VI

MAMMOGRAPHIC GRADES AND AGE AT FIRST CHILD*

Age at first child (years)	Wolfe grade				OR
	N1	P1	P2	DY	
<24					
Controls ($n = 1559$)	170 (11%)	438 (28%)	764 (49%)	187 (12%)	
Pre-cancer cases ($n = 10$)	0	0	7 (70%)	3 (30%)	(1.4—)
⩾24					
Controls ($n = 1921$)	180 (9%)	477 (25%)	951 (50%)	313 (16%)	
Pre-cancer cases ($n = 9$)	1 (11%)	2 (22%)	6 (67%)	0	1.04 (0.2–6.4)

Age at first child <24 years: N1+P1 vs P2+DY, $p = 0.007$ (Fisher's exact test).

* Age at first child unknown for one control.

use of cohort, prevalence, or case/control studies, referral bias, differences in the classification of mammographic patterns and observer variation. Other factors which may have a marked effect on the distribution of parenchymal grades are age, parity, weight and age at first child, and these have rarely been taken into account. There is always the possibility that the different proportions of Wolfe grades in various populations are not due to any of these factors but reflect genuine biological differences.

There is considerable controversy over the degree of risk of breast cancer to women with P2 or DY grades. In general, it appears that studies with the least number of objectionable methodological features show that risk is enhanced (Boyd et al, 1984). In the present study the relative risk associated with P2 DY grades is approximately 4. This figure must be taken with some caution since the number of pre-cancer cases is small, the follow-up time is relatively short, and prevalent and interval cancers have been combined. In addition, Taber and Dean (1982) suggest that the risk in N1 and P1 grades is as high as that in the P2 and DY categories after a 15-year lag-period.

Our results, nevertheless, are in accordance with the generality of other findings and indicate that, in the Guernsey population, a group of women at increased risk of breast cancer can be identified by mammography. The results suggest that Wolfe grades, in conjunction with anamnestic variables, may isolate quite substantial subsets of the potential breast cancer cases. For example, women weighing over 66 kg with P2 or DY grades make up under 20% of the population, yet 65% of our breast cancer cases were found in this group. Their risk level appears high enough to justify considering intensive screening or other intervention strategies. To revert to the original aim of these studies, comparisons of the endocrine status of two groups of women with a fourfold difference in risk might well shed some light on the role of hormones in relation to breast structures (as assessed by mammography) and in the aetiology of breast cancer.

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Book reviews

Radiolabelled Cellular Blood Elements. Pathophysiology, Techniques and Scintigraphic Applications. Ed. by M. L. Thakur, pp. x+429+index, 1985 (Plenum Press, New York), $69.50 (20% higher outside US & Canada).
ISBN 0-306-41935-1

The use of radiolabelled cellular components of blood has emerged as an important tool in understanding their physiological, migratory and pharmacokinetic behaviour. It has also provided an effective diagnostic tool, particularly the use of ^{111}In-labelled platelets for various clinical applications. This rapidly developing field presents challenges and opportunities for researchers with the usual problems of how to assimilate and keep abreast of new information and developments. This book has brought together informative and detailed reviews of all aspects of the subject by leading specialists in the field. The scope of coverage is thorough: separation techniques of various cells, labelling techniques, imaging procedures and clinical evaluation. It also touches upon future possibilities and directions.

The first five articles deal with the pathophysiology, biochemistry and pharmacology of platelets, neutrophils and lymphocytes and also cell isolation techniques and various methods of labelling. This is followed by a comprehensive review of the clinical research and use of ^{111}In-labelled platelets which covers kinetic studies, evaluation in animal models and *in-vivo* quantification and survival studies. It also covers their use in thromboembolism, renal transplants and bypass grafts of blood vessels of various sizes and functions. These are followed by a critical examination of current research and future possibilities for labelling leukocytes by using surface receptors, such as antibodies. Lymphocyte migration studies in humans and granulocyte kinetic studies are outlined, as well as the current state of the art in imaging infections with labelled leukocytes. Radiation doses from the use of the ^{111}In label on various cells are calculated and presented.

This is an excellent reference book for clinicians, scientists and technologists working in the field, a valuable teaching aid and a must for laboratories using labelled blood cells.

H. L. Sharma

Diagnostic Interventions in Nuclear Medicine. Ed. by J. H. Thrall and D. P. Swanson, pp. viii+276, 1985 (Year Book Medical Publishers, Chicago), £44.00.
ISBN 0-8151-8802-1

Unlike interventional radiology, which in general has therapeutic connotations, interventions in nuclear medicine are usually performed to enhance diagnostic information. The number of such interventions is increasing. The editors of this multiauthor text estimate that while 10 years ago less than 1% of nuclear medicine investigations involved interventional procedures, these account for as much as 30% of the workload in some centres at the present time. Such interventions may be physiological, as in cardiac stress testing, or pharmacological, as in hormone suppression tests or diuresis renography.

There is comprehensive coverage of the application of intervention in nuclear cardiology, renal imaging (with particular reference to ureteric obstruction) and adrenal-gland scintigraphy. Other chapters deal with peripheral vascular disease, thyroid disease, the central nervous system, the hepatobiliary system and the gastrointestinal tract, including gastrointestinal haemorrhage. There are also chapters on the related aspects of the way in which concomitant drug administration may interact with radiopharmaceuticals to alter the results of radionuclide studies and on the use of radionuclide techniques to monitor invasive therapeutic procedures, such as arterial perfusion.

Although 18 authors have contributed to the text, there is a pleasing uniformity of style and lack of duplication of material. There is an emphasis throughout on the way that the interventional techniques can enhance the functional information which is fundamental to nuclear medicine. All the chapters contain a wealth of practical information about the techniques described and list extensive references for further reading. The book can be warmly recommended both as a guide to current practice and as a basis and stimulus to further developments in this field.

E. P. Wraight

1986, *The British Journal of Radiology*, 59, 493–497 MAY 1986

The measurement of limb blood flow using technetium-labelled red blood cells

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ABSTRACT

A method for measuring blood flow below the knee during reactive hyperaemia induced by 3 min of arterial occlusion has been developed. Subjects are positioned with lower limbs within the field of view of a gamma camera and pneumatic cuffs are placed below the knees to isolate the blood and induce a hyperaemic response. The remaining blood pool is labelled with $^{99}Tc^m$-labelled red cells. Blood flows have been derived from the initial gradients of time–activity curves and from equilibrium blood sampling. The technique has been validated using a tissue-equivalent leg phantom and peristaltic pump. The method has been applied to a small group of patients with peripheral vascular disease and to normal controls. The mean value ($\pm$SD) of limb perfusion for normal controls was found to be 16.4 ± 3.0 ml/100 ml/min and for patients with intermittent claudication was 5.1 ± 2.6 ml/100 ml/min. Flow measurements are found to correlate with clinical findings and with symptoms. Reproducibility (established by repeated measurements) is high. The method is well tolerated even by patients suffering from rest pain

The major determinant of the severity of symptoms in peripheral vascular disease is the blood flow to the affected region. To an extent this will depend on the degree of arterial narrowing and upon the number and size of collateral vessels which have developed in response to ischaemia.

Non-invasive methods for measurement of blood flow include ultrasonography (Gosling, 1976; Fitzgerald & Carr, 1977) and venous occlusion plethysmography (Whitney, 1953; Kester et al, 1981). Doppler ultrasound may be used to estimate the mean flow in major arteries but does not take account of any collateral vessel formation. Venous occlusion plethysmography, which has a poor signal-to-noise ratio at low flow rates, is subject to a variety of technical errors and artefacts (Figar, 1959) and uses equipment which is not widely available.

Simple methods of assessing arterial insufficiency such as ankle/brachial pressure indices or claudication distance are imprecise and have limited reproducibility.

The use of a freely available, reproducible method of measuring blood flow to the legs would allow more precise grading of patients, would permit quantification of the results of treatment and would aid in differentiating between vascular and non-vascular causes of exercise-induced pain.

Radionuclides have been used previously to study blood flow in patients with peripheral vascular disease by measuring clearance rates of $^{99}Tc^m$ pertechnetate following an intramuscular injection (Cutajar et al, 1971; Angelides et al, 1978) and by first-pass radionuclide arteriography (Oshima et al, 1984). Both methods have proved to be sensitive in detecting peripheral vascular disease, but they do not lend themselves to absolute measurements of flow. A semi-quantitative technique was developed by Cuypers and Merchie (1962), who used a scintillation probe placed over the foot to monitor the arrival of ^{131}I-labelled serum albumin during reactive hyperaemia and produced an index of blood flow based on the wash-in rate following arterial occlusion. In the present report, a technique has been developed for use with a gamma camera to obtain absolute measurements of flow. Pneumatic blood pressure cuffs are placed below the knees and inflated for 3 min to isolate the blood in the lower legs and to induce a hyperaemic response. The remaining blood pool is labelled with technetium. Following the release of the cuffs, the rate of inflow of activity (which depends on limb perfusion) can be measured from the gradient of a time–activity curve generated from that region. Blood samples from the equilibrated blood pool are taken to calibrate the inflow curve so that absolute flow rates can be determined. To validate the method, measurements have been made with a tissue-equivalent phantom of a human leg connected to a peristaltic pump.

The technique has been applied to a small group of patients with peripheral vascular disease and to 10 normal controls. The reproducibility of the method was established by repeated measurements on five subjects.

MATERIALS AND METHODS

Phantom studies

A phantom representing a human leg below the knee was constructed from a cast taken from a volunteer. This was used to vacuum-form a leg cavity using PVC

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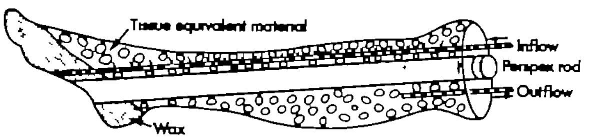

FIG. 1

Section through the leg phantom.

sheets (Fig. 1). A perspex rod, diameter 3 cm, was inserted into the cavity as a geometrical representation of bone and held in place with cement. An inflow tube consisting of 6 mm-diameter polyethylene tube perforated down its length with 1.5 mm-diameter holes radially spaced at 2 cm intervals was inserted. The end of the inflow tube was blocked and held in place by casting it into a layer of wax in the lower part of the foot.

The outflow tube was a short length of polyethylene tube inserted through the top (knee) of the phantom. The cavity was filled with pellets of tissue-equivalent material and the remaining air space filled with water. Transmission profiles obtained using a photon absorptiometer showed the simulated soft-tissue sections of the phantom to have attenuation characteristics within 10% of similar sections taken through a human leg.

A reservoir containing 10 l of water was connected to the inflow of the phantom via a peristaltic pump. The output was collected in a measuring cylinder. The phantom was placed over a large-field gamma camera (Siemens 75 ZLC) fitted with a high-sensitivity, parallel-hole collimator so that the whole of the leg cavity was within the field of view (Fig. 2). Approximately 500 MBq of ^{99}Tc^{m} was added to the reservoir and stirred to ensure equilibration. The pump was switched on and data acquired in 1 s frames for 100 s using an on-line minicomputer (Nodecrest V77). At the end of acquisition, the volume in the measuring cylinder was noted and the flow rate calculated. A 10 ml aliquot of the reservoir fluid was then counted for 2 min on the gamma camera and a background reading was obtained with all sources removed from the room. (These data are required for calibrating the inflow curve.) The procedure was repeated at several different pump speeds allowing for complete decay of the activity in the phantom after each run.

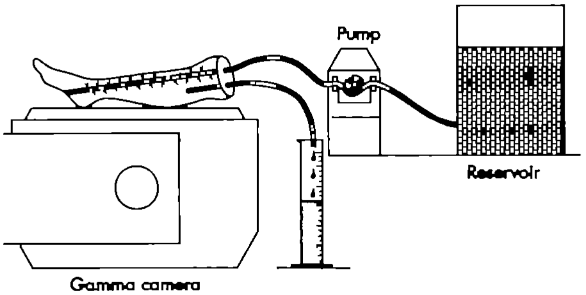

FIG. 2.

Experimental blood-flow measurements in the leg phantom using a gamma camera.

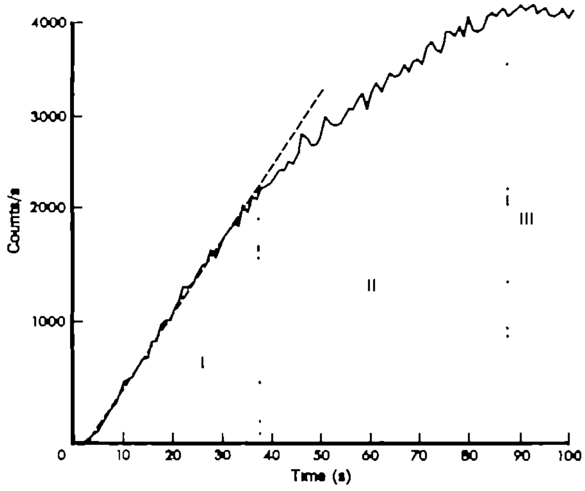

FIG. 3.

Time–activity curve for leg phantom showing the three phases: (I) linear phase, (II) exponential phase, (III) equilibrium phase.

To process the stored dynamic data, a region of interest was drawn to encompass the whole of the phantom and a time–activity curve was generated (Fig. 3). Three distinct phases can be identified in the curve.

(I) *Linear phase:* activity is flowing into the leg at a constant rate and is displacing non-active liquid.

(II) *Exponential phase:* after significant mixing within the leg, a constant fraction of the activity in the leg is replaced by an equal volume of reservoir liquid with a higher specific activity.

(III) *Equilibrium phase:* complete mixing has been achieved and the activity per unit time flowing into the leg is equal to that flowing out.

A least-squares gradient over the linear portion of the curve was calculated. This represents the rate of arrival of activity and is proportional to flow. The constant of proportionality was determined by counting a 10 ml aliquot of reservoir fluid. If this is C counts/s/ml (corrected for background) and the least-squares gradient corrected for self-absorption is G counts/s/s then the flow, F is G/C ml/s. A correction factor for self-absorption is needed to take account of the differences in self-attenuation between the 10 ml aliquot and the leg phantom. This factor was measured on a separate occasion by counting a 10 ml aliquot of ^{99}Tc^{m} on the gamma camera and injecting it into the leg phantom and mixing thoroughly. The leg phantom was then counted for the same time and a correction factor calculated from the ratio of the counts. It was found to be 21%, so in each case the least-squares gradients are scaled by a factor 100/79.

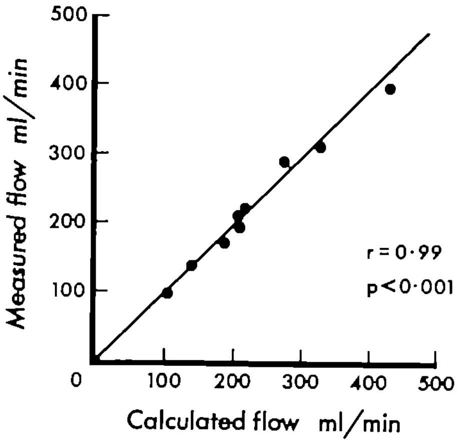

FIG 4.

Flow measurements from leg phantom obtained by direct reading plotted against those obtained from the least-squares gradient over the linear phase of the time–activity curves.

Figure 4 summarises the results obtained by direct measurement (with measuring cylinder and stop watch) and from the gradient of the inflow curves. There is good agreement over the whole range of flows used. The mean difference between these observations was 5.9% and the maximum error 10.6%.

The correlation coefficient between the linear portion of the time–activity curve and the "least-squares" line through the points was greater than 0.99 in all cases, demonstrating that there is insignificant loss of activity from the phantom during the first phase.

Patient studies

The technique has been used on 10 patients with peripheral vascular disease with claudication affecting one or both legs and on 10 normal controls. Measurements were performed simultaneously on both legs. In five subjects (nine limbs) the procedure was repeated to assess the reproducibility of the technique.

Erythrocytes labelled with 500 MBq of ^{99}Tc^{m} were used in the study. Labelling is carried out *in vitro* using the method of Mock and Wellman (1984) and the labelled cell suspension is made up to 5 ml with isotonic saline. A self-absorption correction factor for the patient's legs is obtained by measuring the fractional transmission of γ rays from a ^{57}Co marker source through the thickest part of the calf, lateral to the tibia.

With the patient supine, the legs and feet are positioned on the gamma camera and cuffs 12 cm wide are wrapped around both legs, immediately below the knee (Fig. 5). The upper limit of the camera field of view is marked on the skin with a pen. It is important that all the limb distal to the skin marks is within the camera field of view, so that the venous return from the foot does not augment the arterial flow into the region of interest. Blood pressure is recorded and the cuffs are rapidly inflated to at least 50 mmHg above systolic pressure. The labelled cells are injected into an antecubital vein and allowed to equilibrate. After 2 min 55 s of arterial occlusion, acquisition of 100 frames at 1 s/frame is commenced and a 10 ml blood specimen is taken from the opposite arm. The cuffs are deflated at 3 min (the 5 s lead time is to check that no radioactivity has leaked into the limb prior to deflating the cuffs). After completing the acquisition of flow data from the leg, the patient and all other sources are removed from the room, the blood-pool specimen is counted and the background activity measured. Finally, the leg volumes are measured up to the skin marks using a displacement plethysmograph to enable blood flow (ml/100 ml tissue/min) to be calculated. The stored dynamic data is processed in the same way as the phantom data: a region of interest is drawn to encompass the whole of each limb within the field of view and time–activity curves are generated. Again, the three distinct phases can be identified (Fig. 6).

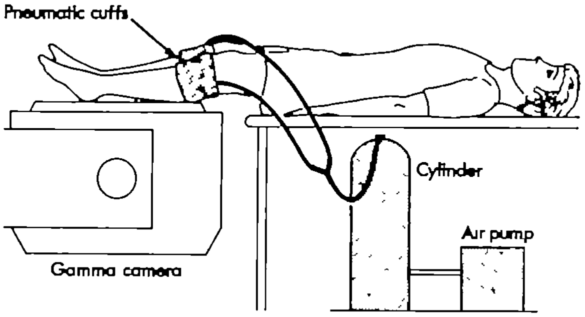

FIG. 5.

Positioning of patients for blood-flow measurements.

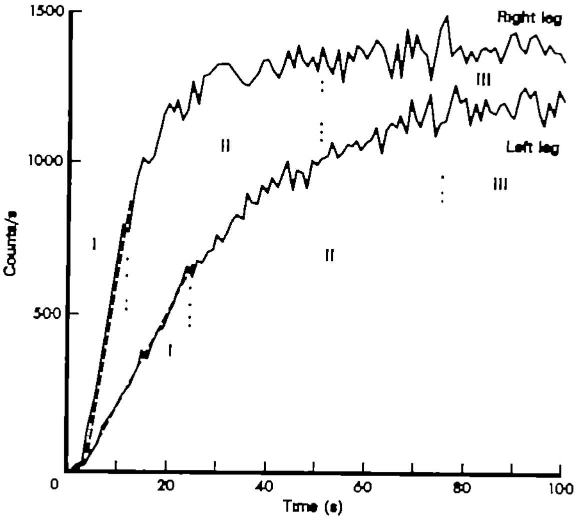

FIG. 6.

Typical time–activity curves obtained from a patient with a left-side arterial occlusion.

TABLE I

PERFUSION MEASUREMENTS IN NORMAL CONTROLS

Control	Limb flow (ml/min)		Limb volume (l)		Limb perfusion (ml/100 ml/min)	
	R	L	R	L	R	L
1	386	395	2.9	3.0	13.3	13.2
2	357	325	2.3	2.3	15.5	14.1
3	449	488	2.8	2.9	16.0	16.8
4	520	510	2.6	2.6	20.0	19.6
5	296	300	2.2	2.2	15.2	15.4
6	518	540	2.4	2.5	21.6	21.6
7	403	445	2.6	2.6	15.5	17.1
8	428	428	2.1	2.2	20.4	19.4
9	271	259	2.2	2.2	12.3	11.8
10	382	372	2.5	2.6	15.3	14.3

Mean perfusion = 16.4 ± 3.0 ml/100 ml/min

TABLE II

REPRODUCIBILITY OF PERFUSION MEASUREMENTS IN CONTROLS

Limb	Perfusion (ml/100 ml/min)	
	Occasion 1	Occasion 2
1	13.3	13.5
2	20.0	19.1
3	19.6	19.5
4	15.3	13.4
5	15.1	13.6
6	4.6	4.4
7	6.5	6.7
8	13.3	14.1
9	11.1	11.1

$R = 0.99$, $p < 0.001$.

The least-squares gradients over the linear portions of the curves are calculated and corrected using the self-absorption factor for the leg phantom (21%). A further factor is needed to take account of the variations between patient limbs and the leg phantom. This is calculated from the fractional transmission of radiation from a ^{57}Co marker source in the leg phantom and in the patient. The differences between the two have always been less than 10%. The lower-limb flow is then calculated for each leg using Equations (1) and (2)

$$F_R = G_R/C \times 60 \text{ ml/min} \quad (1)$$
$$F_L = G_L/C \times 60 \text{ ml/min} \quad (2)$$

where G_R,G_L counts/s/s are the least-squares gradients corrected for self-absorption for the right and left legs respectively, and C is the activity of the blood-pool specimen corrected for background (counts/s/ml).

RESULTS AND DISCUSSION

Table I summarises the results of flow measurements on 10 normal controls. The mean value (±SD) of perfusion for this group was found to be 16.4 ± 3.0 ml/100 ml/min. This is significantly lower than values obtained by strain-gauge plethysmography (Barendsen, 1980) and gravimetric plethysmography (Kester et al, 1981) which are 23.4+4.5 and 43.5+17.2 ml/100 ml/min respectively. This is to be expected since the major part of the hyperaemic flow will go to muscle. The radionuclide method averages perfusions over the whole of the lower limb including foot and ankle, which have a relatively small proportion of muscle, whereas the strain-gauge method monitors volume changes over the calf. Gravimetric plethysmography includes a large volume of muscle above the knee, which will yields higher values of perfusion.

The reproducibility of the technique was assessed by repeating the measurements on five subjects (nine limbs). Table II summarises these results and shows the method to be highly reproducible ($R = 0.99$, $p < 0.001$).

The results of measurements on patients with peripheral vascular disease are shown in Table III. The severity of symptoms were determined by interviewing the patient at the time of the scan and were assessed on a four-point scale. It can be seen that the symptomatic legs all have lower perfusion than the non-symptomatic legs. In most cases, the severity of symptoms and arteriography findings correlate with the degree of impaired flow. However, in Case 3, arteriography showed a right-sided occlusion of the superficial femoral artery and in Case 7 arteriography showed an occlusion of the right external iliac artery. Perfusion measurements and symptoms of these limbs appeared normal. The overestimation of the extent of disease by arteriography has been observed previously (Giargiana et al, 1973) and the presence of substantial collateral vessels noted in both these cases could account for the discrepancy. Interestingly, the only diabetic patient (Case 8) had a history of bilateral claudication, but arteriography showed no major vessel disease and limb perfusions were only just below the normal range.

The self-absorption coefficient used in the flow calculation was found to be relatively constant at about 20% and this figure could be adopted in clinical studies without appreciable error.

It might be expected that the non-active blood returning to the pool would dilute it and change the activity input rate to the leg. This effect is found to be insignificant since the correlation coefficient of the least-squares fit to the linear part of data was found to be greater than 0.99 in all cases. The length of the linear phase will depend upon venous capacity and the duration of peak hyperaemic flow. In severe claudicants it was found to be up to 40 s, whereas in normal controls it was typically 12 s. With 1 s frames there are sufficient data points to calculate the gradient of the regression line with a high degree of confidence in both groups.

CONCLUSION

This is a simple, low-cost, widely available method of measuring lower-limb blood flow. It gives accurate and

TABLE III

PERFUSION MEASUREMENTS IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE

Case	Limb flow (ml/min)		Limb volume (l)		Limb perfusion (ml/100 ml/min)		Symptoms intermittent claudication		Arteriography (dominant lesion)	
	R	L	R	L	R	L	R	L	R	L
1	64	169	2.5	2.5	2.6	6.8	+ + Foot ulcer	+ + +	F3	F2
2	143	43	2.9	2.9	4.9	1.5	+ +	+ + +	I3	F3
3	392	81	2.3	2.4	17.0	3.4	0	+ + +	F3	F3
4	156	273	2.6	2.4	6.0	11.4	+ +	0	F2	0
5	194	76	2.0	2.0	9.7	3.8	0	+ + +	0	F3
6	113	207	2.2	2.3	5.1	9.0	+ + +	+ +	F3	F3
7	248	88	2.5	2.6	9.9	3.4	0	+ + +	I3	I3F3
8	243	216	2.4	2.2	10.1	9.8	+ +	+ +	0	0
9	75	86	2.5	2.6	3.0	3.3	+ +	+	*	*
10	93	82	1.9	1.9	4.9	4.3	+ + +	+ + +	F3	F3

Symptoms: 0 = no symptoms, + = mild claudication, + + = moderate claudication, + + + = severe claudication.
Arteriography findings: F = femoral disease, I = iliac disease, 0 = normal, 1 = mild stenosis, 2 = severe stenosis, 3 = occlusion.
*Bilateral femoral-popliteal clinically occluded grafts.

reproducible measurements of flow and is well tolerated even by patients suffering from severe rest pain.

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Book reviews

Interventional Real-time Ultrasound. Ed. by Hiroki Watanabe and Masatoshi Makuuchi, pp ix+189, 1985 (Igaku-Shoin, Tokyo), £53.75.
ISBN 0–89640–112–X (New York)
4–260–14112–0 (Tokyo)

This slim volume describes the various interventional techniques that can be performed under ultrasound control. The authors begin with a short resumé of the history of interventional ultrasound and then describe the technology of biopsy needles and of the special transducers that can facilitate accurate needle placement. An interesting chapter on experiments on dog kidneys to assess the damage caused by varying the shape and profile of biopsy needles concludes the more theoretical chapters. The rest of the book describes in detail the clinical application of interventional ultrasound. Not all of the techniques are standard practice yet in the United Kingdom.

The chapters vary enormously in quality; some are, quite frankly, very poor. Even the better chapters are not of a quality one would expect from a British or American textbook, in part due to the somewhat individual English. The book cannot be recommended to the general reader especially as it costs over £50.00. However, it would be useful if it were available in the larger institutional libraries for reference for those who wish to undertake some of the newer techniques for the first time

L. A. Berger

The Pediatric Spine. Ed. by David S. Bradford and Robert M. Hensinger, pp. viii+528+index, 1985 (Georg Thieme Verlag, Stuttgart), DM 240.
ISBN 0–86577–126–X

This is a comprehensive review of paediatric spinal disease, written by a consortium of distinguished orthopaedic surgeons. An introductory section deals with development of the vertebral column, spinal biomechanics, clinical and radiological evaluation of spinal disease and the problem of back pain in children. Major sections then follow on inflammation, trauma, tumours spinal deformity, spondylolisthesis and techniques in spinal surgery. The book is profusely illustrated, wide ranging and has a good bibliography to each section. This is essentially a clinical update, by surgeons, for surgeons. As always, however, radiologists can learn from their clinical colleagues and this volume provides an excellent insight into the clinical management of conditions frequently inadequately understood by radiologists.

D. G. Shaw

Iatrogenic Disorders of the Fetus, Infant and Child, Vol. II. Ed. by E. G. Kassner, pp. xxiii+477+index, 1985 (Springer-Verlag, Berlin), DM 560.
ISBN 3–540–96005–8

This is the second volume of a treatise delineating the numerous iatrogenic conditions of childhood. The catalogue of horrors and disasters continues with the residual problems and complications of surgery. There are chapters concerning the airway, thorax and diaphragm, cardiac surgery, gastrointestinal and abdominal surgery, urology, including a whole chapter on diversion and undiversion, and finally two chapters about the potential disasters of orthopaedic surgery and neurological surgery. The treatment is comprehensive, illustrations are numerous and clear and there is an extensive bibliography. The editor is to be congratulated on producing such an illustrative and timely reminder of the adverse potential of our profession. The publishers have also produced companion volumes about iatrogenic gastrointestinal and iatrogenic thoracic complications and the series will provide a detailed and salutary review and source of reference.

D. G Shaw

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Lack of discernible effect of diagnostic ultrasound on the chromosomes of cord blood lymphocytes exposed *in utero*

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ABSTRACT

The levels of either sister chromatid exchanges or chromosome breakage (as assayed by the frequency of micronuclei) in cord blood lymphocytes from a total of 62 babies were analysed. The exposure of these babies to ultrasound during gestation was determined retrospectively from medical records and the data reclassified accordingly. No correlation was seen between the levels of chromosome breakage, as measured by these two end-points, and exposure to ultrasound.

Although ultrasound is now widely used for diagnostic purposes during pregnancy, concern persists regarding its safety (Anonymous, 1984). Since the initial reports indicating an increased level of chromosome breakage in human lymphocytes irradiated *in vitro* (MacIntosh & Davey, 1970, 1972), many further studies, including those of the original investigators (MacIntosh et al, 1975) have failed to confirm this result.

For some genotoxic treatments, sister chromatid exchange (SCE) analysis is more sensitive in detecting chromosome damage than is the analysis of chromosome breakage (Perry & Evans, 1975). Amongst 11 reports of the analysis of SCE frequency in mammalian cells exposed to ultrasound *in vitro* (Table I), two studies have reported induction of SCEs by exposure to diagnostic levels of ultrasound (Liebeskind et al, 1979; Haupt et al, 1981). Others have failed to reproduce these results using similar conditions (Miller et al, 1983; Brulfert et al, 1984; Ciaravino et al, 1984). All studies of *in vivo* exposure (Table II) which have either investigated chromosome aberrations or SCE induction after diagnostic ultrasound have given negative results. However, some of these studies have used fibroblasts or amniocytes (Ikeuchi et al, 1973; Zheng et al, 1981; Lundberg et al, 1982) which require several cell divisions to establish adequate cell numbers. This may have prevented the detection of genetic damage by allowing repair or dilution of initial lesions or selection against damaged cells. Studies of cord, fetal, or neonatal lymphocytes have been directed predominantly at an analysis of the effects of fetal heart monitoring by Doppler ultrasound on chromosome breakage. These have demonstrated a lack of chromosome-breaking activity by ultrasound. No studies on the frequency of SCEs in lymphocytes of *in utero* exposed humans have been reported. This observation prompted us to analyse, retrospectively, exposure to ultrasound in a sample of babies from which we had previously obtained data on the incidence of SCEs and chromosome breakage in cord blood lymphocytes.

We have been obtaining cord blood samples from the

TABLE I

SUMMARY OF INVESTIGATIONS ON CHROMOSOME BREAKAGE AND SCE INDUCTION BY *IN VITRO* EXPOSURE TO ULTRASOUND

System	Result	Reference
Chromosome aberrations		
HL	+	Macintosh & Davey, 1970, 1972
HL	–	Bobrow et al, 1971; Buckton & Baker, 1972, Boyd et al, 1971; Coakley et al, 1971, 1972, Abdulla et al, 1972; Macintosh et al, 1975, Rott & Soldner, 1973
CHO	–	Wegner et al, 1980
CH	–	Hill et al, 1972
SCEs		
HL	+	Liebeskind et al, 1979, Haupt et al, 1981
HL	–	Miller et al, 1983; Morris et al, 1978; Wegner & Meyenburg, 1982; Brulfert et al, 1984; Ciaravino et al, 1984
HeLa	–	Liebeskind et al, 1979
CHO	–	Wegner et al, 1980; Wegner & Meyenburg, 1982; Barnett et al, 1982
HF	–	Barass et al, 1982

HL, human lymphocytes; CHO, Chinese hamster ovary; CH Chinese hamster, HF, hamster fibroblasts, HeLa, human fibroblast line

TABLE II

REVIEW OF EFFECTS ON CHROMOSOME BREAKAGE AND SCE INDUCTION FOLLOWING *IN VIVO* EXPOSURE TO ULTRASOUND

System	Treatment	Result	Reference
Chromosome aberrations in humans			
Fetal fibroblasts	Diagnostic	–	Ikeuchi et al, 1973
CBL	Diagnostic	–	Boyd et al, 1971
Fetal blood and adult blood	Diagnostic, fetal heart monitoring	–	Abdulla et al, 1971
Cord blood, adult blood	Fetal heart monitoring	–	Watts & Stewart, 1972
Neonatal blood	Fetal heart monitoring	–	Lucas et al, 1972
Adult blood	Therapeutic	–	Stella et al, 1984
Chromosome aberrations in animals			
Mouse fetus	> Diagnostic	–	Mannor et al, 1972
CH BM	Therapeutic	–	Galperin-LeMaitre et al, 1973
Mouse spermatocytes	> Diagnostic	–	Lyon & Simpson, 1974
Hamster BM	Therapeutic	–	Levi et al, 1974
Mouse BM	Therapeutic	–	Harkanyi et al, 1978
SCEs in humans			
Amniocytes	Diagnostic	–	Zheng et al, 1981; Lundberg et al, 1982
HL	Therapeutic	+	Stella et al, 1984
SCEs in animals			
Mouse embryos	> Diagnostic	–	Au et al, 1982

CBL, cord blood lymphocytes; CH BM, Chinese hamster bone marrow; HL, human lymphocytes.

Royal Sussex County Hospital since 1979 as part of a programme to develop short-term tests of genetic damage which could be used to detect possible causes of childhood malignancies (Cole & Henderson, 1982; Cole et al, 1982; Aghamohammadi, 1983). The samples used in the present study were obtained and analysed for SCEs between November 1979 and June 1980 and for micronuclei between July 1980 and May 1982. We present here the results of analysis of SCE frequencies and micronuclei in cord blood lymphocytes. The analysis of micronucleated lymphocytes has previously been shown to be a rapid and sensitive method of assessing chromosome damage (Aghamohammadi et al, 1984).

MATERIALS AND METHODS

Sister chromatid exchange analysis

Cord blood samples were collected into syringes containing at least 100 units heparin (BDH) per ml of blood. Whole blood cultures were set up within 18 h of collection. Cultures containing 0.2 ml blood, 0.2 ml phytohaemagglutinin (Wellcome), 10 μM bromodeoxyuridine, 10 μM deoxycytidine (Sigma), 2 ml fetal calf serum (Flow Laboratories), 150 units/ml penicillin and 150 μg/ml streptomycin (Gibco) and 6 ml Ham's F10 (Flow Laboratories) were incubated in the dark for 72 h. Metaphase cells were arrested by the addition of colchicine (1 μM final concentration) for 3 h and chromosome preparations made by conventional techniques. The method of Goto et al (1978) was used to obtain sister chromatid differentiation. Twenty cells, each with 46 chromosomes, were analysed from each sample.

Micronuclei

Mononuclear blood cells were separated from whole blood and cultures were set up containing 0.5×10^6–1×10^6 cells per ml in media as outlined above, but without bromodeoxyuridine and with newborn calf serum (Gibco) instead of fetal calf serum and incubated for 92–96 h. The cells were harvested by a technique developed to preserve the cytoplasm, stained and analysed as previously described (Aghamohammadi, 1983; Aghamohammadi et al, 1984). At least 2000 lymphocytes with intact cytoplasm from each sample were analysed for the presence of micronuclei.

Exposure to ultrasound

Medical records were analysed to provide information on exposure to ultrasound *in utero*. Scans, when done, had been with either a 3.5 MHz linear array or a 3.5 MHz sector scanner. The duration of each scan was not recorded. The stage of gestation and number of scans were recorded. Possible confounding variables such as exposure to smoking, birth weight and gestational age at birth, drugs taken during pregnancy and the mother's occupation were also extracted.

RESULTS

The SCE frequency in samples from 16 unexposed babies was compared with samples from 27 babies exposed to one or more scans (Table III). The data were log-transformed, and no difference between the means of each set and the control sample were found ($p > 0.05$ in all cases). An increase in the mean log-transformed SCE frequency in the exposed group of 0.139 above the

TABLE III

Effect of exposure to ultrasound on SCE frequency in cord blood lymphocytes

No of scans	Sample size	Mean ± SD	Range
0	16	4.2 ± 1.1	3.1–6.6
1	10	4.2 ± 0.7	3.5–5.8
2	12	4.1 ± 0.8	2.9–5.2
3	4	4.4 ± 1.5	3.1–6.6
4	1	5.6	

mean transformed SCE frequency of 1.418 in the non-exposed population would have been detected with 95% confidence in this sample. This corresponds, approximately, to a 15% increase above control levels. An analysis of "high-frequency cells" based on the statistical method of Carrano and Moore (1982) was also applied. This may be more sensitive than the comparison of means where only a subpopulation of cells has been damaged, or only a proportion of damaged cells remains due to dilution with non-exposed cells. In our population, a sample with more than three cells with nine or more SCEs is significantly different from the population. There was no difference between the number of individuals with such high-frequency cells in the exposed or non-exposed population. In Table IV, the time of exposure to ultrasound is tabulated. Where babies were exposed to more than one scan, only the time of exposure to the most recent scan is considered. No significant differences between these groups were seen. The mean SCE value for babies from smoking mothers (4.4 ± 1.1) was not significantly different from the value for babies from non-smoking mothers (4.1 ± 1.0).

The mean frequency of micronucleated lymphocytes per 1000 cells from nine babies exposed to ultrasound *in utero* (3.4 ± 2.7) and the mean frequency in 10 non-exposed babies (2.9 ± 2.6) were not significantly different ($t_{(17)} = 0.72$, log-transformed data) (Table V). An increase in the mean log-transformed micronucleus frequency of the exposed group of 0.835 above the mean log-transformed frequency of the unexposed group of 0.694 would have been detectable in this sample with 95% confidence. This corresponds, approximately, to a 2.3-fold increase above control levels. The baby with the highest mean frequency of micronucleated lymphocytes (9.5 per 1000) had had more scans (four) than any other baby, but the mother of this baby was also a smoker and a diabetic. The second highest value (8.5 per 1000) was found in a sample from a baby who had not been exposed to ultrasound, but whose mother was also a smoker. The overall incidence of micronucleated lymphocytes in babies of smoking mothers (3.7 per 1000, 10 samples) was not significantly elevated above non-exposed babies (2.7 per 1000, eight samples; $t_{(16)} = 0.86$).

TABLE IV

Effect of interval between exposure to ultrasound and birth on SCE frequency in cord blood lymphocytes

Exposure time	Sample size	Mean ± SD
Not exposed	16	4.2 ± 1.1
First trimester	4	4.5 ± 1.0
Second trimester	7	3.9 ± 0.8
Third trimester	14	4.9 ± 1.0
< 1 week before birth	2	4.3

TABLE V

Mean frequency of micronucleated lymphocytes per 1000 cells in individual cord blood samples

Non-exposed individuals	Exposed individuals	
0.5	1	(one scan)
1	1.5	(one scan)
1	3	(one scan)
1	3	(one scan)
1	1	(two scans)
3	2.5	(two scans)
4	3.5	(two scans)
4	6	(two scans)
5	9.5	(four scans)
8.6		

Discussion

This study involved an analysis of chromosome damage followed by a retrospective evaluation of ultrasound exposure Therefore the results are free from bias. Neither chromosome breakage nor SCE showed any change as the result of exposure to diagnostic ultrasound *in utero*. However, there are some limitations to this study. Circulating lymphocytes are at the G_0 stage of the cell-cycle and a cell-cycle stage-specific effect of ultrasound would not be detectable. Other studies have not indicated that such an effect exists (Wegner & Meyenburg, 1982; Stella et al, 1984). Another possible limitation is whether lesions (if they were induced by ultrasound) would be detected at birth. Information on the persistence of lymphocytes formed in early fetal life has been obtained from *in utero* exposed survivors of the Hiroshima bombings (Bloom et al, 1968). Cells with unstable chromosome aberrations have been detected in the circulation of such individuals, including those exposed during the first trimester, up to 20 years after the exposure. This suggests that both the micronucleus and SCE assays in cord blood lymphocytes should be capable of detecting genetic damage induced in early pregnancy, providing such lesions are not repaired in G_0 lymphocytes. The only information which exists on the persistence of lesions induced by ultrasound has been obtained by monitoring the SCE levels in lymphocytes of patients exposed to therapeutic ultrasound (Stella et al, 1984). Although SCE levels were elevated throughout the course of therapy, SCE frequencies had returned to normal within 3 months after exposure, suggesting that circulating lymphocytes may be able to repair such lesions or that damaged cells had been removed. Although it cannot definitely be excluded that diagnostic ultrasound did induce lesions, which were either repaired or were not detectable at birth due to cell loss and dilution with unexposed cells, it should be noted that several babies exposed to ultrasound in the week preceding birth did not show elevated SCE or micronucleus frequencies.

Therapeutic ultrasound involves the use of higher intensities of radiation than diagnostic ultrasound. Since therapeutic ultrasound induces SCEs *in vivo*, it is possible that diagnostic ultrasound induces chromosome damage at lower levels, but that such low-dose effects are not detectable by presently available short-term tests.

In summary, while our study supports the belief that diagnostic ultrasound in pregnancy does not induce detectable chromosome damage, in view of the possibility of short-lived lesions induced by ultrasound, the reports of induction of SCEs in two *in vitro* studies (Liebeskind et al, 1979; Haupt et al, 1981) and a report of SCE induction by therapeutic ultrasound in human lymphocytes exposed *in vivo* (Stella et al, 1984), it would appear to be worthwhile to study SCE and micronucleus levels in fetal lymphocytes shortly after ultrasound exposure. It may be feasible to obtain sufficient lymphocytes for these studies at the same time as fetal blood samples are collected for determination of genetic abnormalities.

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Book review

Radiopharmaceuticals and Labelled Compounds 1984. IAEA Conference Proceedings, Tokyo, October 22–26, 1984. International Atomic Energy Agency, pp. 560+index, 1985 (IAEA, Vienna), 1140 Austrian Schillings
ISBN 92-0-040085-X

This publication contains the proceedings of a conference on radiopharmaceuticals and labelled compounds organised by the IAEA in co-operation with the Japan Radioisotope Association, held in Tokyo in October 1984 The previous conference organised by the IAEA on this topic was held in Copenhagen in 1973 and, by comparing the proceedings of both meetings, it is clear that a great deal of progress has taken place in the intervening 11 years In particular, there appears to be a shift away from the discussion of the production of radionuclides to the preparation of specific radiolabelled compounds This is borne out by many papers which describe the use of sophisticated separation techniques (HPLC) and careful chemical characterisations of these compounds (NMR). Some papers have also reflected the increasing involvement of modern technology with discussions of remote handling and computer-controlled processes.

The papers presented (70) are subdivided into nine topics, with some overlap, six of which contain invited papers. The principle topics include the production of radionuclides and generators (nine papers), the chemistry, synthesis and application of labelled compounds (21 papers) and a section on biodistribution studies (11 papers).

The invited papers go a long way towards fulfilling the aims of the conference in "reviewing recent developments and to provide an international forum for discussion and dissemination of information". However, unlike the Copenhagen meeting, the frequently enlightening discussion following each presentation has not been published. Furthermore, some authors did not provide titles along with the references and this omission was also unfortunate. There are some good reviews: one, by A. P. Wolf on the application of small cyclotrons and the production of positron emitters, contains some rare glimpses of the future (albeit for the affluent West). There is also an interesting contribution (by W. Wolf) on kinetic studies with radiopharmaceuticals, which attempts to encourage all of us to look more closely at the biotransformation of injected radiopharmaceuticals. A reminder is given by K. Kristensen that the effects of regulations are not all negative, an example being quality assurance, which has added much to the quality of our investigations

The majority of the remaining articles and abstracts are short research papers which are in a mixture of languages. In conjunction with the omission of a subject index, the usefulness of this part of the volume to a full international readership must be limited.

S. WATERS

Case reports

Gastric emphysema demonstrated by computed tomography

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(*Received August 1985*)

Gas in the wall of the stomach is a rare occurrence which can be well demonstrated radiologically. The nomenclature of intramural gastric gas has been confusing, despite a reasoned approach to its classification, proposed initially over 20 years ago (Keyting et al, 1961) and recently emphasised (Kussin et al, 1982; Kowal et al, 1982; Lee & Rutledge, 1984). The purpose of the present report is to describe a case of gastric emphysema demonstrated by computed tomography (CT) and to reinforce the current classification based on aetiology.

CASE REPORT

A 74-year-old man was admitted with a 2-week history of vomiting and a 1-week history of progressively deepening jaundice. He had lost more than 10 kg in weight. He had been in good health previously and there was no relevant past medical history. On examination he was jaundiced and there was 4 cm smooth, tender hepatomegaly. No other abnormality was present. There was no succussion splash. Initial investigations showed a hypochloraemic, hypokalaemic alkalosis. The blood urea and creatinine levels were significantly elevated. All of these abnormalities were corrected with intravenous fluid replacement. Ultrasound examination showed dilatation of the intrahepatic bile ducts and of the common hepatic duct. The distended, fluid-filled stomach was evident as a transonic epigastric mass but no further information was obtained. Computed tomography was performed, initially without preparation. The tomogram (Fig. 1) showed the typical linear lucency of gastric wall gas which was confirmed by transaxial sections. The gastric wall was outlined by a thick, gas-density stripe (Fig. 2). Following gastric aspiration, CT was repeated with oral contrast preparation (Fig. 3). This showed a reduction in the thickness of the gastric wall lucency but also demonstrated a soft-tissue mass lying in the region of the common bile duct, immediately above the head of the pancreas and obstructing the pylorus. The dilated bile ducts were confirmed but no other abnormality was seen. Upper gastrointestinal endoscopy demonstrated normal gastric mucosa and with an extrinsic soft-tissue mass lying above and behind the pylorus, causing complete pyloric obstruction. Biopsies taken from within the pylorus showed no evidence of malignancy.

Laparotomy demonstrated a malignant mass lying above the head of the pancreas and involving the common bile duct which was too locally extensive to be considered resectable. A cholecystojejunostomy and gastroenterostomy were performed. The patient made an uneventful post-operative recovery and was allowed home. A plain radiograph of the upper abdomen demonstrated no evidence of stomach wall gas at the time of discharge. Biopsies taken at surgery confirmed adenocarcinoma, which was considered to be of bile-duct origin.

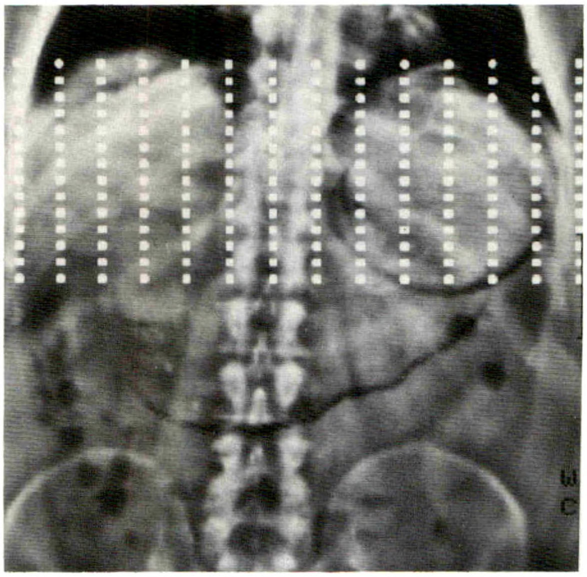

FIG. 1.

Computed tomogram demonstrating linear stomach-wall gas-density lucency.

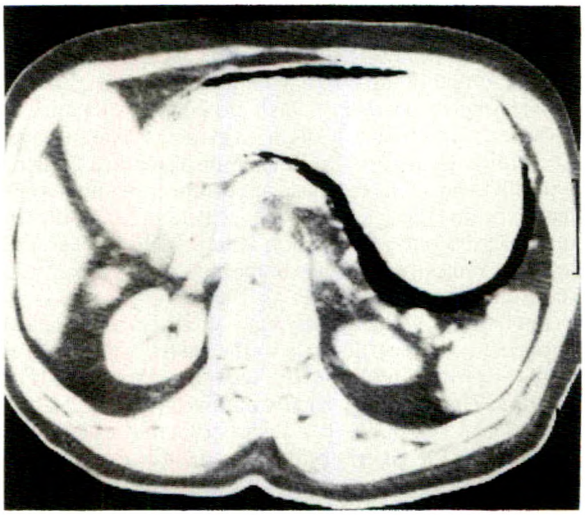

FIG. 2.

Transaxial section at low window level showing thick stripe of gastric wall gas.

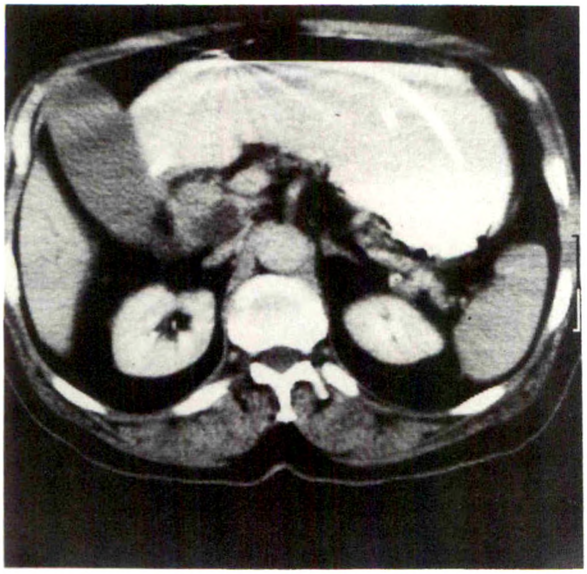

FIG. 3.

Post-contrast section showing irregular mass adjacent to pylorus and common bile duct.

DISCUSSION

Gas in the wall of the stomach has traditionally been regarded (Lumsden, 1956) as being due to: (1) emphysematous gastritis, (2) interstitial gastric emphysema or (3) cystic pneumatosis.

Emphysematous gastritis is an acute infection of the gastric wall with gas-forming organisms, usually *E. coli* or *C. welchii* (Henry, 1952). It occurs as a result of trauma, including surgery, infarction and ingestion of toxic chemicals, particularly caustics, in alcohol abuse and occasionally as a result of simple gastroduodenitis (Udassin et al, 1984). The clinical picture is one of sudden onset of abdominal pain, fever and vomiting progressing to death in a high proportion of patients. Stricture formation can occur in patients who survive. The radiological appearance in emphysematous gastritis typically shows a mottled appearance of numerous lucencies in the gastric wall, which is a result of multiple, discrete gas bubbles, although the appearance can sometimes be of a linear lucency of gas density in the stomach wall (Berens et al, 1968).

Interstitial gastric emphysema shows a radiological appearance of linear lucency in the gastric wall which is similar to that occasionally seen in emphysematous gastritis. The patient is usually relatively well, in distinct comparison to emphysematous gastritis, but usually has some cause for gastric outlet obstruction or proximal small-bowel obstruction (Kay-Butler, 1962). A similar appearance can be seen in patients who have undergone upper gastrointestinal endoscopy, particularly in the presence of gastric distension (Myhre & Wilson, 1948; Katz et al, 1972).

Cystic pneumatosis (Lumsden, 1956) occurs in patients with pulmonary disease in a similar way to colonic pneumatosis and is asymptomatic. The radiological appearance of cystic pneumatosis is similar to that of emphysematous gastritis. The confusion has arisen in the distinction between interstitial gastric emphysema and pneumatosis. Others have misclassified these two conditions with the consequence that there has been no concensus regarding the distinction between the two (Kay-Butler, 1962; Udassin et al, 1984). Because of the similarity of the radiological appearance of gas in the stomach wall, irrespective of aetiology, a clinical classification is essential. The current classification depends on the basic tenet that gas either is formed within the stomach wall (emphysematous gastritis) or enters the stomach wall from outside (gastric emphysema) as a consequence of some other condition. Gastric emphysema is classified by aetiology as being traumatic, obstructive or pulmonary. Traumatic gastric emphysema is a consequence of instrumentation or surgery. Obstructive emphysema is due to gastric outlet obstruction with associated gastric dilatation and it is thought that gas enters the submucosa or subserosa via mucosal tears during vomiting. Pulmonary gastric emphysema is due to obstructive airway disease and is thought to develop as a consequence of covert mediastinal air passing retroperitoneally and ultimately entering the wall of the intestine via the mesentery.

The current case is, therefore, classified as one of obstructive gastric emphysema due to pyloric obstruction from the adjacent, extrinsic malignant mass with associated vomiting. The gastric mucosa was seen to be normal at endoscopy, which was undertaken after the demonstration of the stomach wall gas. We should like to reinforce the suggestion that the term "cystic pneumatosis" be deleted in reference to stomach wall gas and that the nomenclature of emphysematous gastritis and gastric emphysema be adopted.

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Ultrasonically guided fine-needle biopsy for histological sampling of suspect parathyroid tissue

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Several reports have confirmed the ability of ultrasound in localising enlarged parathyroid glands (Butch et al, 1985). However, a general problem with this technique has been the difficulty of distinguishing nodular thyroid lesions from abnormal parathyroid tissue (Karstrup & Hegedüs, 1986).

We report a case in which a parathyroid adenoma was correctly diagnosed in a patient with severe hypercalcaemia by use of percutaneous ultrasonically guided fine-needle biopsy for histological examination.

CASE REPORT

A 66-year-old male presented with loss of weight, fatigue, polyuria and polydypsia. Two weeks previously he had an episode of transient aphasia and facial paralysis. Since the age of 30 years he had been treated with digitalis because of atrial fibrillation. Physical examination revealed enlargement of the thyroid gland with a palpable nodule in the left lobe. Further notable findings were hypermobility of the joints.

On admission, serum calcium was 4.38 mmol/l (normal 2.20–2.70 mmol/l), ionised calcium 2.43 mmol/l (normal 1.13–1.24 mmol) and phosphate 0.64 mmol/l (normal 0.80–1.60 mmol/l). Serum creatinine was normal. Electrocardiography revealed atrial fibrillation and a radiograph of the chest showed enlargement of the heart.

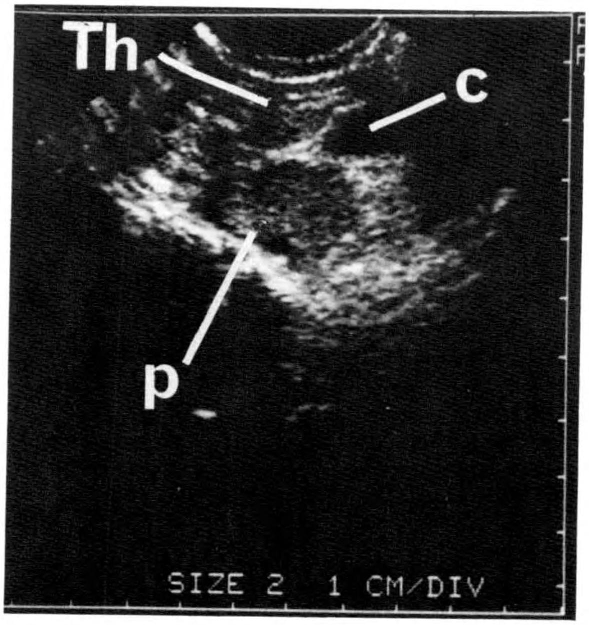

FIG. 1.

An oblique scan of the neck showing a well defined parathyroid adenoma (p) located deep to the lower pole of the right thyroid lobe (Th). C indicates the common carotid artery.

In spite of intensive medical treatment, including intravenous infusion of calcitonin and mithramycin, severe hypercalcaemia persisted. A real-time ultrasonic examination of the neck using a 5 MHz transducer revealed an enlarged multinodular thyroid gland. Located posteriorly and deep to the lower pole of the right thyroid lobe, ultrasonography revealed a 25 mm × 16 mm × 18 mm, well defined nodule isoechoic to the thyroid gland, containing cystic areas (Fig. 1). Ultrasonically guided fine-needle (23 gauge, 0.6 mm) aspiration of the abnormal area was carried out. The aspirated material was sent for parathyroid hormone (PTH) analysis (Karstrup et al, 1985) and for cytological examination. Furthermore, a 23-gauge histological biopsy (Surecut) was performed (Torp-Pedersen et al, 1984). The patient had no discomfort during or following the procedures.

The cytological evaluation could not determine a parathyroid origin. The results of the PTH analysis were not available pre-operatively because of the time needed for analysis (3 weeks). The histological material contained small

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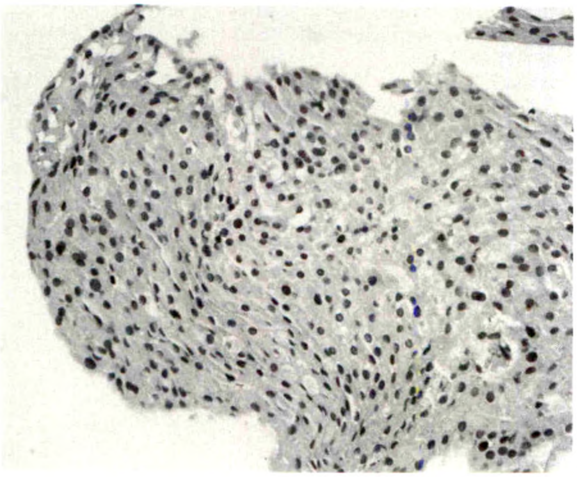

FIG. 2.

Parathyroid tissue obtained by histological needle biopsy (haematoxylin and eosin ×200).

fragments of parathyroid tissue composed entirely of chief cells (Fig. 2).

At subsequent surgery, the ultrasonic finding was confirmed and a parathyroid adenoma was removed. Post-operatively, serum calcium concentrations returned to normal levels.

DISCUSSION

Recent studies indicate that ultrasonic examination can be utilised for the visualisation of enlarged parathyroid glands and can, thus, be of value in the pre-operative investigation of patients with hyperparathyroidism (Butch et al, 1985). However, the demonstration of a cervical mass is not tissue-specific. Nodular thyroid lesions may show the same pattern of echoes resulting in false positive findings. In fact, some studies show as much as 40% of patients with primary hyperparathyroidism having thyroid lesions of surgical significance (Laing et al, 1969; Karstrup & Hegedüs, 1986). In order to confirm the nature of the tissue seen by ultrasonography, preliminary reports have suggested the use of percutaneous fine-needle aspiration for cytological evaluation (Solbiati et al, 1983; Gooding et al, 1985) or for PTH determination (Doppman et al, 1983; Karstrup et al, 1985). In the present case neither of these latter interventional techniques was of any benefit.

We have used ultrasonically guided fine-needle aspiration for parathyroid tumours for 2 years. The determination of endocrine origin of the aspirated cells has not been difficult but, so far, our experience is too limited to enable differentiation between parathyroid and thyroid cells with certainty in the majority of cases. We note, of interest only, one recent case (Charboneau et al, 1983) where percutaneous fine-needle biopsy for histological sampling was successful in diagnosing a parathyroid adenoma pre-operatively. In this case the cytological examination was also inconclusive.

Despite the small size of the histological biopsy in the present case, the diagnosis of parathyroid tissue was straightforward. Percutaneous histological biopsies of suspected parathyroid tissue have, however, generally not been carried out, probably for fear of complications, since histological biopsies traditionally have been carried out with large-bore needles. By performing the biopsy with a 23-gauge Surecut needle, the advantages of fine-needle biopsy, *i.e.* low complication rate, are combined with the advantages of large-bore biopsy, *i.e.* material for histological examination (Torp-Pedersen et al, 1984).

Although some centres report cytological identification of parathyroid tissue, the value of fine-needle aspiration biopsy remains doubtful, since no study of diagnostic reproducibility has been carried out and others have not been able to reproduce their results. Probably, the cytological evaluation requires a great deal of skill and experience (Zajicek, 1974). The histological evaluation is much easier and more reliable for the ordinary pathologist (Torp-Pedersen et al, 1984).

Fine-needle aspiration biopsy for PTH analysis is probably very accurate, but has, at least in our centre, the disadvantage of being very time-consuming (3 weeks). The time needed for the histological evaluation, including fixation, paraffin embedding and so on, is routinely 24 h.

In conclusion, ultrasonically guided fine-needle biopsy of suspect parathyroid tissue may secure a reliable tissue diagnosis and thereby possibly aid in the clinical decision of the subsequent treatment. Furthermore, it may be helpful for patients requiring re-exploration, those with ectopic parathyroid tissue and those requiring a shortened surgical procedure.

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Arteriohepatic dysplasia

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Arteriohepatic dysplasia (Alagille syndrome, Watson–Alagille syndrome, syndromatic hepatic ductular hypoplasia) is a syndrome complex of chronic intrahepatic cholestasis and pulmonary artery stenosis combined with other somatic defects such as dysmorphic facies, eye and skeletal abnormalities, and hypogonadism (Watson & Miller, 1973; Alagille et al, 1975). The basic pathology of the liver is stated to be congenital absence or hypoplasia of interlobular bile-ducts (Dahms et al, 1982). In spite of several interesting radiographic findings, the syndrome has been mentioned only once in the radiological literature (Rosenfield et al, 1980). The purpose of this paper is to describe radiographic and hepatic sonographic findings in three patients with this syndrome.

CASE REPORTS

Case 1. An 18-year-old man had been jaundiced from birth until the age of 9 years, when jaundice resolved spontaneously. An operative cholangiogram performed at 3 months of age had shown patent extrahepatic and major segmental bile-ducts. Liver biopsy showed a sparseness of intrahepatic bile-ducts. He also displayed an "odd" triangular facies and had hypercholesterolaemia, xanthomatosis and a pulmonary stenotic murmur. A pulmonary angiogram (Fig. 1) showed peripheral pulmonary arterial stenoses and "butterfly" third, fifth and ninth thoracic vertebrae.

Case 2. A 15-year-old girl had been continuously jaundiced from birth. On examination she had hepatosplenomegaly and abnormal liver-function tests. At the age of 1 year, an operative cholangiogram had shown patent extrahepatic and major segmental bile-ducts and a liver biopsy had shown sparse, small intrahepatic bile-ducts. She also had an "odd" facies, was mildly mentally retarded, and had a pulmonary stenotic murmur. A skeletal survey showed uniform osteopenia and a retarded bone age (Fig. 2). An abdominal ultrasound scan showed evidence of diffuse parenchymal liver disease with a hypoechoic mass at the medial aspect of the right lobe (Fig. 3). A technetium sulphur-colloid scan showed increased activity at the site of the mass in the right lobe (Fig. 4) and a liver biopsy showed cirrhosis of the liver with a regenerative nodule.

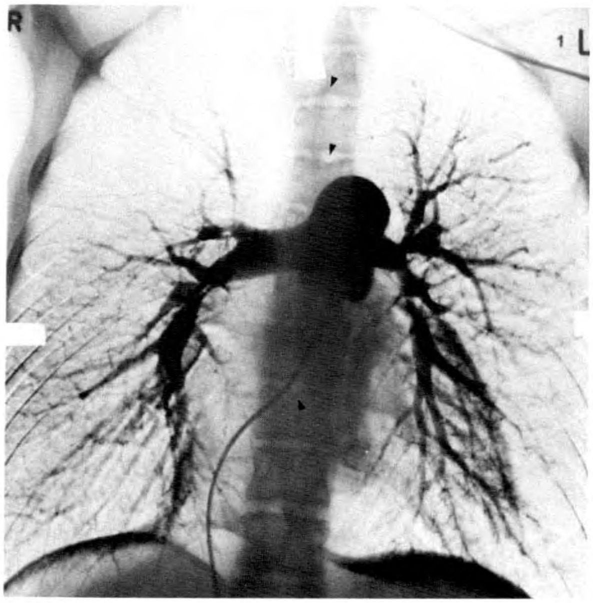

FIG. 1. *Case 1*.

A pulmonary angiogram shows peripheral pulmonic stenoses and "butterfly" thoracic vertebrae (arrowheads).

Case 3. The 12-year-old brother of Case 2 also had neonatal jaundice and a pulmonary stenotic murmur. Although his illness was less severe than that of his sister, he had hepatosplenomegaly and disturbed liver-function tests. A

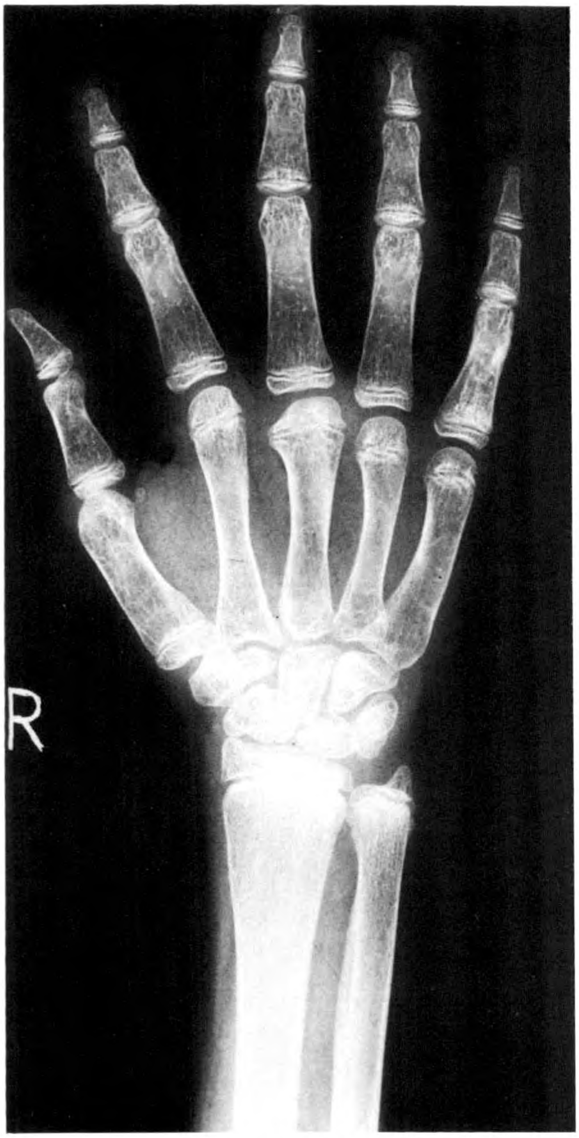

FIG. 2. *Case 2.*

A hand radiograph shows uniform osteopenia and a bone age of 9 or 10 years, compared with the chronological age of 15 years.

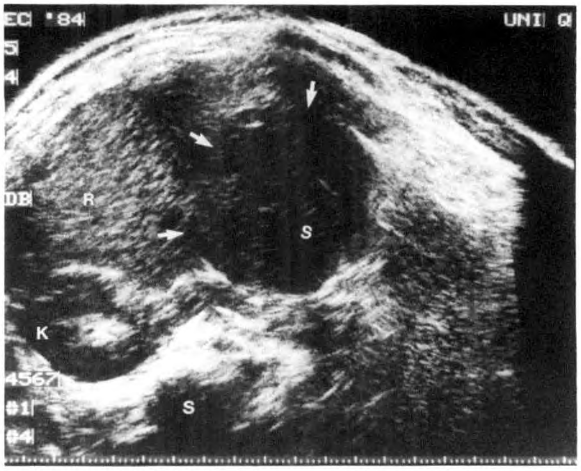

FIG. 3. *Case 2.*

Transverse hepatic sonogram shows a hypoechoic mass (arrows) at the medial aspects of the right lobe (K = right kidney, R = right hepatic lobe, S = spine).

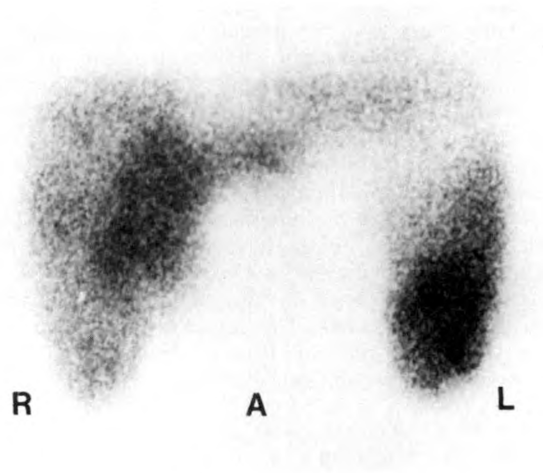

FIG. 4. *Case 2.*

A sulphur-colloid liver scan shows relatively increased activity at the site of the mass.

skeletal survey showed osteopenia and delayed skeletal maturity. An abdominal ultrasound scan showed moderate, diffuse liver disease and splenomegaly (Fig. 5).

DISCUSSION

Neonatal jaundice is a usual feature in arteriohepatic dysplasia with varying degrees of severity and duration. Ultrasound may be helpful to rule out congenital cystic disease and extrahepatic biliary obstruction; however, hepatobiliary scintigraphy or operative cholangiography may also be necessary to exclude obstructive causes of jaundice such as biliary atresia (Markle et al, 1980). There is little information regarding the ultrasound findings in this syndrome (Rosenfield et al, 1980; Dahms et al, 1982). From our cases we found that in the older patients ultrasound showed varying degrees of diffuse increase in echogenicity and loss of fine detail consistent with parenchymal liver disease. Cirrhosis with regenerative nodules and portal hypertension was also present. The ultrasonic finding of a mass lesion in Case 2 was confusing initially. The demonstration of increased activity on the sulphur-colloid radionuclide scan was helpful in excluding malignancy. Although CT

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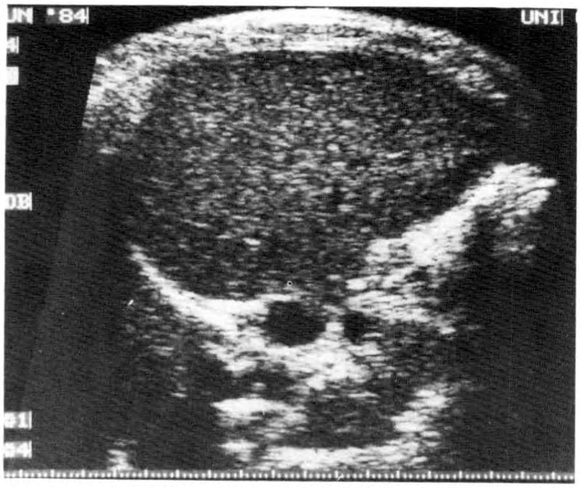

FIG. 5. *Case 3.*

An oblique hepatic sonogram shows diffuse increase in echogenicity and loss of fine detail consistent with diffuse parenchymal liver disease.

confirmed the ultrasonic evidence of localised hepatic enlargement, it did not assist in characterising the lesion, which was isodense before and after the injection of a contrast agent.

Peripheral pulmonic stenosis is the most common cardiovascular malformation in this syndrome and is sometimes associated with intracardiac lesions (Greenwood et al, 1976; Riely et al, 1979). On chest radiographs, the cardiac size and pulmonary vascularity depend upon the severity of the lesions; both may be normal if stenosis is mild.

Previous reports of skeletal findings in arteriohepatic dysplasia have included different types of vertebral malformation, osteopenia, short distal phalanges, foreshortening of the ulna and retarded bone age (Watson & Miller, 1973; Alagille et al, 1975; Riely et al, 1979; Dahms et al, 1982). Among these findings, a "butterfly" vertebra is very common and it is, therefore, important to look for this on the chest radiograph.

Patients with arteriohepatic dysplasia come to medical attention due to either liver or heart problems. Skeletal anomalies are common and, in combination with other findings, may suggest the diagnosis.

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Solution to a knotty biliary drainage problem

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The standard technique for percutaneous transhepatic biliary drainage in our institution and as described in the literature is successive dilatation of the liver tract and biliary system with tapered-tipped dilators until the proper drainage catheter can be inserted (Teplick et al, 1984). We report a case in which the guide-wire became knotted in the duodenum and could not be removed through the standard catheters or tapered-tipped dilators.

CASE REPORT

A 57-year-old man presented with recent onset of obstructive jaundice. Transhepatic cholangiography showed obstruction high in the common hepatic duct which, on biopsy, proved to be metastatic from the prostate. This was considered to be unresectable and the patient elected to have a biliary endoprosthesis. During insertion, the guide-wire (HSF Torque 0.038, Cook Inc., Bloomington, Indiana, USA) twisted in the duodenum, knotted and could not be removed through the tapered-tipped dilators. The knot was closed as tight as possible by pulling against the dilator which was then removed and replaced with a coaxial dilating system (Biliary

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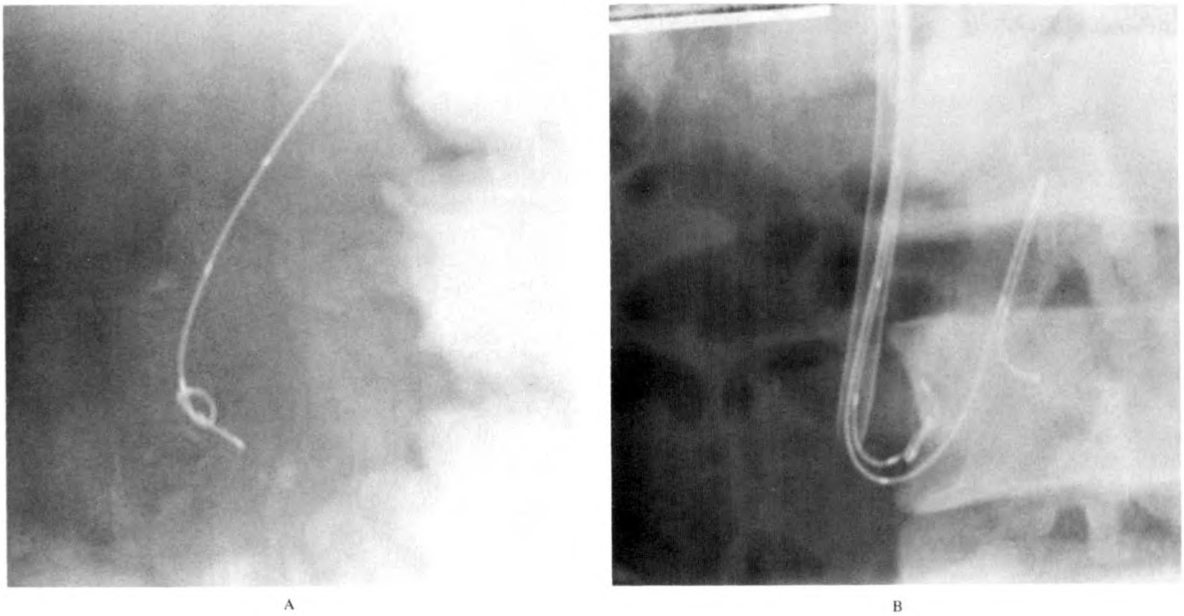

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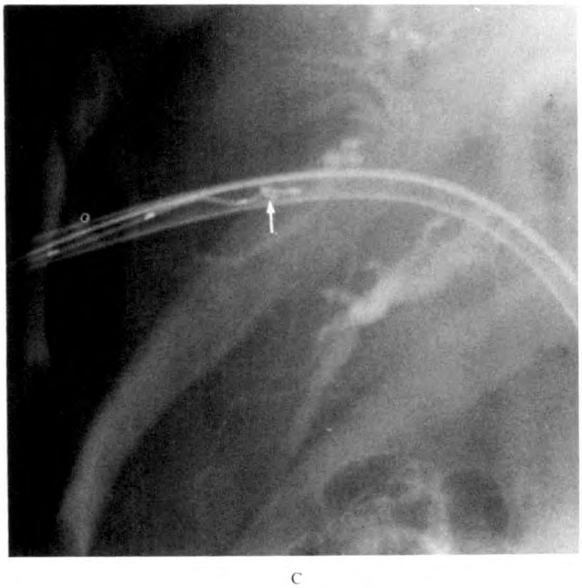

C

FIG. 1.

(A) The guide-wire is knotted. The original tapered-tipped dilator was removed. Note the blastic bone metastases from carcinoma of the prostate. (B) The system was coaxially dilated to size 16 F. The inner dilators were removed, leaving the 16 F dilator in place. A second guide-wire was inserted. (C) The knotted guide-wire (arrow) was removed through the 16 F dilator. The dilator was then removed, leaving the second guide-wire in place.

Stone Removal Dilator Set, Cook Inc., Bloomington, Indiana, USA). Coaxial dilators are not tapered; this allowed us to insert a second guide-wire into the duodenum as well as to remove the knot. It was necessary to dilate to 16 F before the knotted guide-wire could be extracted (Fig. 1). Continuity was maintained by inserting the second guide-wire and the endoprosthesis was inserted successfully.

DISCUSSION

The complications from percutaneous transhepatic biliary drainage are well known (Berk et al, 1982). However, technical difficulties encountered during biliary drainage which may result in increased complication or failure rates are infrequently reported. Creating a knot in the guide-wire is, in our experience, an unusual technical problem. However, there is the possibility of forming a knot because, often, a considerable length of the guide-wire is inserted in the duodenum to prevent dislodgement. The guide-wire often becomes looped and could potentially knot.

Extraction of the knotted wire would not have been possible without a coaxial system. Alternatives would have been to try to extract the wire through the liver tract or cut the wire and allow it to pass through the gastrointestinal tract. Either alternative would have resulted in loss of access to the ductal system and if the liver tract could not be renegotiated, the procedure would have to be terminated or started again.

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Case reports

Skeletal-muscle haemangioma presenting as an abdominal mass

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Skeletal-muscle haemangiomas are relatively common lesions and are usually regarded as representing congenital vascular hamartomas. They constitute 0.8% of all haemangiomas (Chauhan & Baird, 1973). Only 8% of the cases in the literature were diagnosed pre-operatively (Scott, 1957). We describe a case of skeletal-muscle haemangioma occurring in the anterior abdominal wall of a 9-month-old infant in which ultrasound examination was of value in establishing the pre-operative diagnosis.

CASE REPORT

A 9-month-old male infant was noted by his parents to have an abdominal mass which gradually increased in size over a period of 2 months. There were no symptoms referable to the mass and the infant was otherwise healthy and developing normally. He was the fourth child of unrelated parents and the pregnancy and delivery were uneventful. Physical examination revealed a 10 cm × 5 cm firmly nodular mass in the right upper quadrant of the abdomen. The mass was clinically inseparable from the liver and was initially diagnosed as a liver tumour. Haemoglobin was 11.4 g/dl, with a leucocytosis of $12.2 \times 10^6/\text{mm}^3$. Special investigations including liver function tests, immunoglobulins and urine catecholamines gave normal results. Serum alpha-fetoprotein level was lower than 25 μg/dl.

The ultrasound examination (Fig. 1) revealed a highly echogenic, solid mass lying in the anterior abdominal wall. The borders were not clearly defined and it was separating and infiltrating the muscle planes. The mass was limited by the peritoneum and did not extend into the peritoneal cavity. The liver and other intra-abdominal viscera were normal. The plain abdominal radiograph (Fig. 2) confirmed that the mass was extrinsic to the peritoneal cavity and, because of the soft-tissue lucency and highly echogenic nature, it was thought to be a lipoma.

Excision of the mass, including a 1 cm margin of normal tissue, was carried out under general anaesthesia. This left a full-thickness defect of the anterior abdominal wall measuring 15 cm × 7 cm. The underlying abdominal viscera were normal. The defect was repaired by the insertion of a patch of prolene mesh. The wound was closed with suction drainage to the subcutaneous tissue. The post-operative course was complicated by mild wound sepsis which settled with antibiotic therapy.

Macroscopic examination showed an ill-defined mass with a central, slit-like haemorrhagic cavity and irregular edges radiating into the surrounding muscle and soft tissues. Histopathological examination revealed a vasoformative lesion of capillary type. In many areas, the lesion consisted of solid islands of endothelial cells devoid of lumina. Other areas showed unequivocal vessels with small but patent, blood-filled lumina lined by cells similar to those seen in the solid areas. The vascular process infiltrated through muscle bundles (Fig. 3) and through fat. Nuclei were plump and mitotic figures were seen, but there was no multilayering of the endothelial cells; there were no hyperchromatic or multinucleate cells and areas of necrosis were not seen. The features were those of a haemangioma of skeletal muscle. Excision was complete.

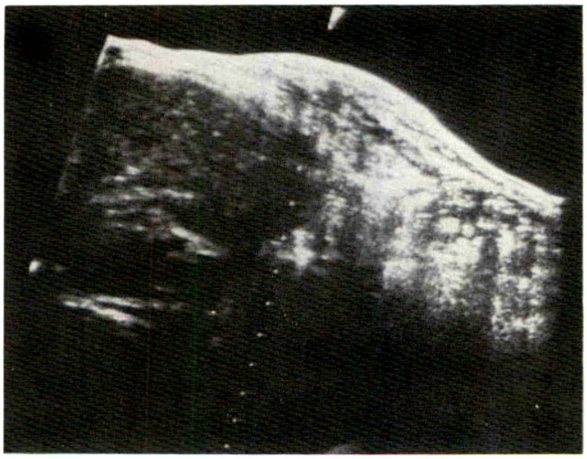

FIG. 1.

Supine longitudinal ultrasound scan 4 cm to the right of the midline. A highly echogenic, solid mass is shown separating the planes of the anterior abdominal wall. Normal liver lies beneath and separate from the mass.

DISCUSSION

Skeletal-muscle haemangiomas appear to be relatively common lesions. Scott (1957) collected 393 histologically proven cases, including two of his own, while Allen and Enzinger (1972) reviewed a series of 89 cases. Most authors believe that these haemangiomas represent congenital vascular hamartomas. They have been observed in all age groups from a newborn infant to a 65-year-old man, but most are discovered in childhood and adolescence and over 85% have occurred in the first three decades of life. Sex incidence is equal and all races may be affected. Allen and Enzinger (1972) subdivided these lesions into three groups: one composed predominantly of small-sized vessels, of which the present case is an example; another in which large vessels predominate; and a third, mixed group

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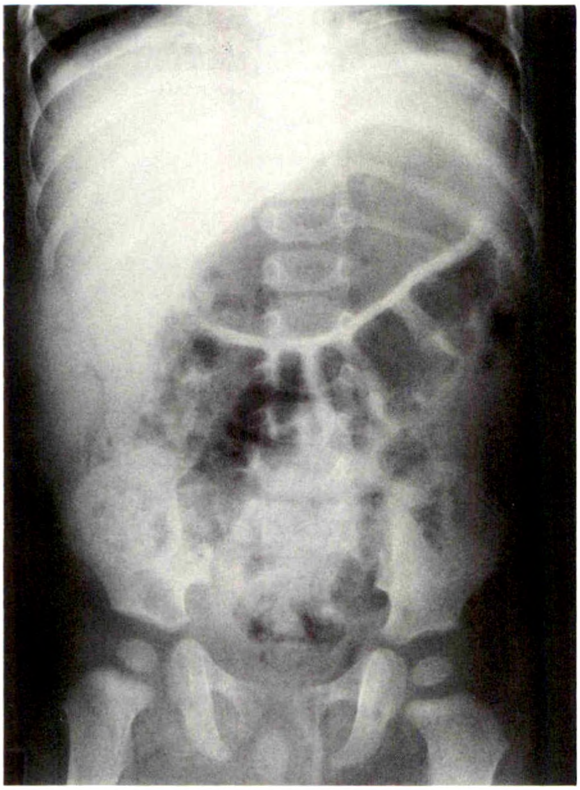

FIG. 2.

Plain abdominal radiograph demonstrates a soft-tissue mass indenting the pre-peritoneal fat line on the right.

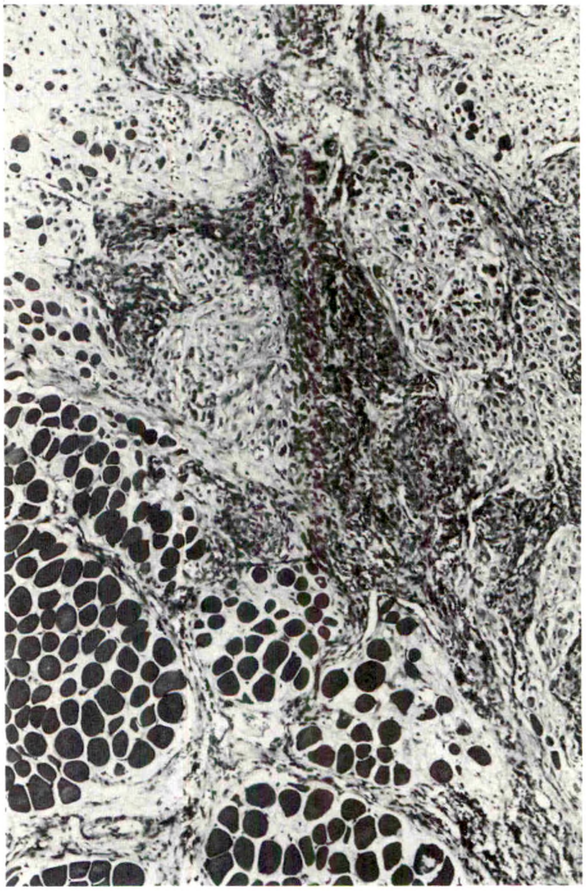

FIG. 3.

Mainly solid area of tumour containing some vascular spaces surrounding and destroying muscle bundles at the top and infiltrating muscle bundles at the bottom (haematoxylin and eosin, × 75).

with large and small vessels in approximately equal proportions. Thirty-two per cent of the small-vessel haemangiomas occurred in the trunk, 30% in the head and neck, and 23% in the upper limb, while only 15% occurred in the lower limb, the most common location for the large-vessel type. In the series of Allen and Enzinger (1972), the correct diagnosis was not suspected in any of the cases before microscopic examination.

Ultrasound can be used very successfully in the evaluation of superficial masses, especially in the delineation of the extent of the mass (Leopold, 1980). The high-resolution real-time scanner is valuable in evaluating these lesions and in many cases may be the only applicable imaging modality.

Sonography in our patient revealed that the tumour was not, as clinically suspected, a liver mass but localised it to the anterior abdominal wall. Multiple sonolucent areas separated by thin septa and complex areas of varying echodensity are suggestive of a mixed lymphangiomatous–haemangiomatous lesion. Our patient had a lesion which exhibited none of these characteristics but was mainly echodense and involved only the abdominal musculature. Abdominal-wall rhabdomyosarcomas have been described but they are echolucent on sonography. The highly echodense nature of the mass in our patient suggested that it was either fat, blood (recent haemorrhage) or fibrosis.

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Case reports

Calcified post-traumatic renal pseudotumour

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Post-traumatic renal calcification is a well recognised but rare entity first described by Abbott (1894). A number of reports have since detailed the plain radiographic, urographic and arteriographic changes that may be seen (Colston, 1932; Daniel et al, 1972; Watt & Penry, 1973; Babaian et al, 1978; Sniderman et al, 1979; Oberschulte-Beckmann & Schnitzler, 1981), but the computed tomographic (CT) and ultrasonic appearances remain undescribed. We wish to report a case in which a full radiological evaluation, including CT and ultrasound, was undertaken and to highlight the difficulty which exists in distinguishing this benign entity from other renal abnormalities, in particular, renal-cell carcinoma.

CASE REPORT

A 23-year-old man presented in the emergency room with an influenza-type illness. The only significant prior medical history was an episode of abdominal trauma at about the age of 9 years which had necessitated hospital admission for a 2-week period because of persistent haematuria. This had eventually settled without the need for surgical intervention. He was discharged and since then had remained well until his current admission. Examination of the abdomen revealed a mass in the right upper quadrant which appeared to be partly calcified on a subsequent plain abdominal radiograph (Fig. 1). Excretory urography confirmed that the mass was renal in origin with associated displacement of the pelvicalyceal system (Fig. 2). Ultrasound demonstrated an echogenic upper-pole mass without evidence of cyst formation. The calcification visible radiographically was located posteriorly and cast an acoustic shadow (Fig. 3). Arteriography demonstrated a dual arterial supply with displacement and stretching of the upper-pole vessels around an avascular mass involving the middle and upper-regions of the kidney (Fig. 4). However, there was no neovascularity. Subsequent CT (Fig. 5) demonstrated an upper-pole mass extending beyond an area of curvilinear calcification which was situated posteriorly. There was no

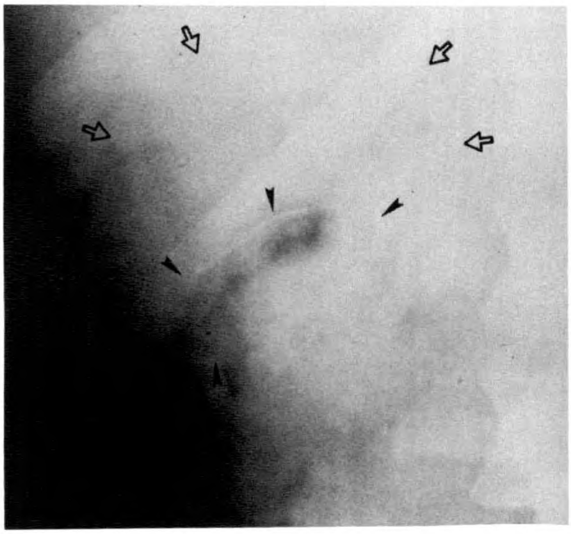

FIG. 1.

Detail of right upper quadrant. Curvilinear calcification (arrowheads) in association with a mass lesion in the upper pole of the kidney (arrows) is clearly shown.

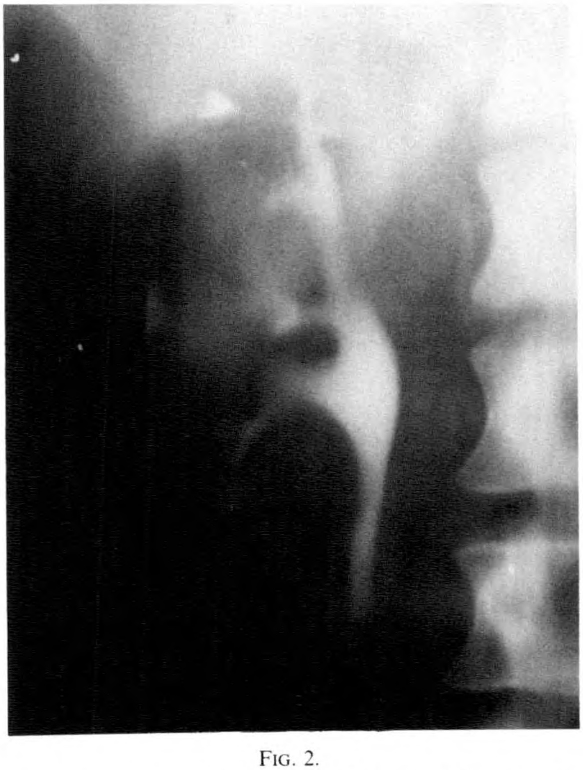

FIG. 2.

Excretory urogram. This tomographic cut delineates the displacement of the middle and upper-pole calyces by the central mass lesion.

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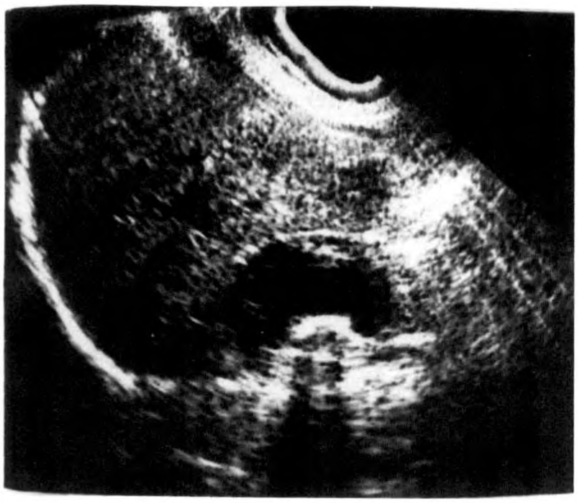

FIG. 3.

Longitudinal ultrasound scan. The upper pole of the kidney is enlarged and an acoustic shadow is cast by the calcification posteriorly.

evidence of a cyst. In view of the failure to exclude renal neoplasia, a subsequent nephrectomy was undertaken from which the patient made an uneventful recovery. The removed kidney (Fig. 6) contained a 4 cm × 3 cm × 3 cm cyst in the mid-kidney containing sero-sanguineous fluid and lined by a heavily calcified wall. Histologically, the cyst wall was composed of thick, fibrous tissue with foci of ossification. There was no evidence of neoplasia and the changes were suggestive of previous renal trauma.

DISCUSSION

Renal trauma may rarely give rise to long-term changes within the kidney. Dystrophic calcification, atrophy, infarction, renal artery aneurysm and traumatic cyst formation have all been described (Gregg, 1968). However, considering the relative frequency of renal trauma, the incidence of post-traumatic renal calcification is surprisingly low. In a review of 2709 renal mass lesions collated over a 10-year period, 111 were found to be calcified but only one case was attributed to renal haematoma (Daniel et al, 1972).

Calcification within renal mass lesions is most commonly due to renal-cell carcinoma and occurs in

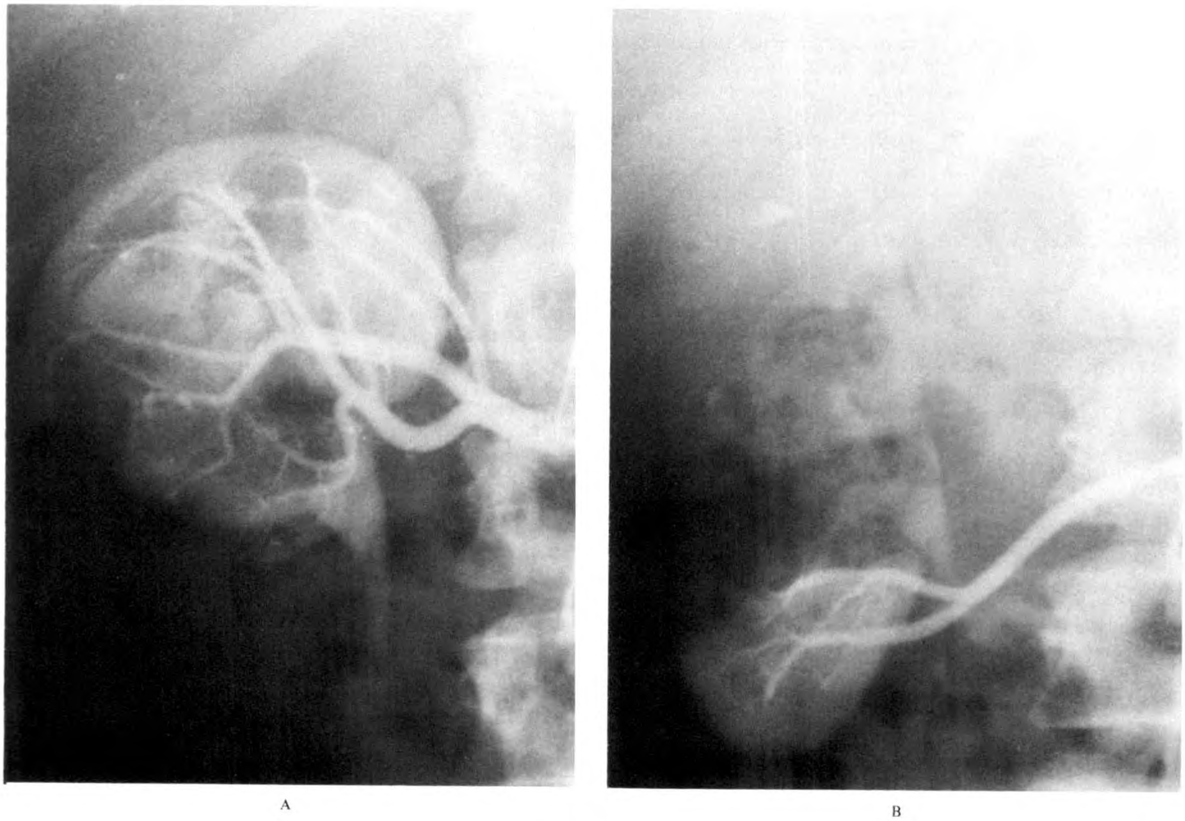

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FIG. 4.

(A, B) Selective upper- and lower-pole angiography. There is an avascular middle section with no evidence of tumour neovascularity.

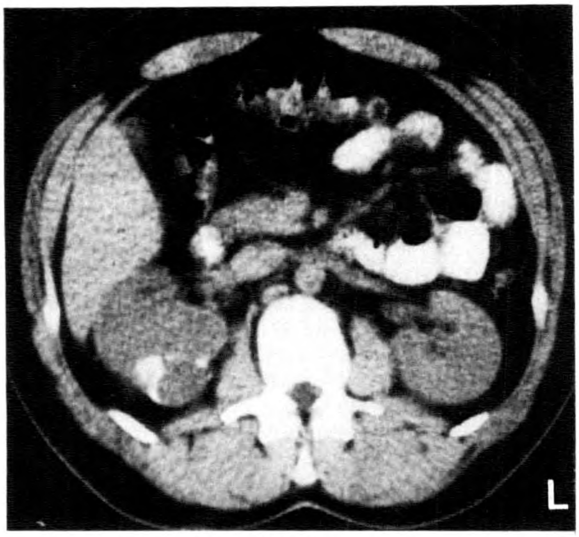

FIG. 5.
Computed tomography scan without contrast (L + 50, W 500). The bulky nature of the right renal mass is delineated, with calcification, predominantly curvilinear in nature, lying posteriorly within it. Note the extension of the soft-tissue mass beyond the area of calcification.

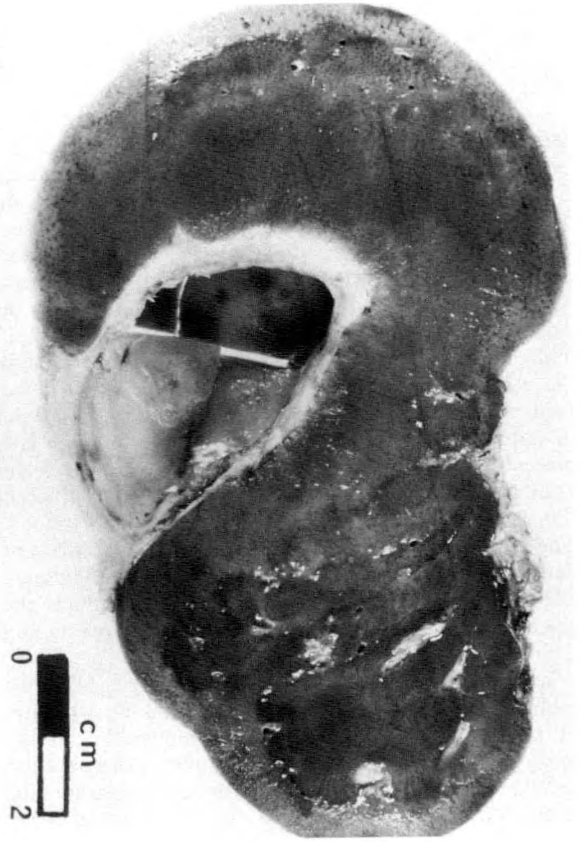

FIG. 6.
Pathological specimen. The cyst is clearly shown in the mid-kidney with associated distortion of normal renal architecture.

about 10% of such cases (Daniel et al, 1972). It is found in 1–2% of simple renal cysts. Other, rarer causes of calcified renal masses in adults include xanthogranulomatous pyelonephritis, metastatic disease, adenomas and hydatid disease. Therefore, when calcification is visualised in association with a renal mass lesion the predominant concern is the exclusion of malignancy.

Post-traumatic renal calcification may be either perirenal or intrarenal. Colston (1932) described six cases of post-traumatic calcification, only one of which appeared to be intrarenal. In that instance the calcification had a combined curvilinear and punctate appearance. This mixed pattern of calcification in intrarenal haematomas would appear to occur frequently when such changes arise: similar appearances have been described by others (Babaian et al, 1978; Sniderman et al, 1979; Oberschulte-Beckmann & Schnitzler, 1981). In contrast, the calcification in perirenal haematomas, which occur more frequently, would appear to be more typically curvilinear in nature. This appearance, which has also been noted radiographically (Colston, 1932; Watt & Penry, 1973; Babaian et al, 1978), is probably due to calcification in the wall of a haematogenous cyst that develops following an episode of perirenal haemorrhage. Although the calcified cyst wall in this patient appeared to have a smooth, curvilinear pattern on plain radiographs, subsequent CT demonstrated irregular thickening of the cyst wall in places.

Attempts to distinguish benign from malignant renal disease on the appearance of the calcification have not proved of value (Sniderman et al, 1979). Calcification within malignant renal mass lesions is commonly punctate and irregular in appearance, but smooth, rim-like calcification is also well recognised (Simpson, 1966; Kikkawa & Lasser, 1969; Sniderman et al, 1979). The location of the calcification may be of more value in distinguishing benign from malignant renal disease. Centrally located calcification is almost always associated with malignancy, whereas peripheral calcification is more likely to be due to benign disease, although malignancy is still responsible for 20% of such cases (Daniel et al, 1972). A reliable distinction, therefore, between benign and malignant renal disease cannot be made on the appearance or location of the calcification.

Angiographic differentiation of benign and malignant renal mass lesions is of great value. Malignant renal lesions display a characteristic neovascularity in 95% of cases (Watson et al, 1968). However, 5–10% of cases are hypovascular or avascular, and diagnosis in such instances is more difficult. When calcified, over 70% of renal carcinomas are said to be either hypovascular or avascular (Sniderman et al, 1979). It is possible that the

1986, *The British Journal of Radiology, 59,* 518–519

avascular nature of the tumour predisposes to necrosis with subsequent calcification. The partially calcified and avascular nature of this lesion meant that a renal malignancy could not be excluded.

Computed tomography and ultrasound have both been used in the elucidation of calcified renal mass lesions (Yiu-Chiu et al, 1981; Weyman et al, 1982). Computed tomography facilitates the cross-sectional display of the calcification in relation to the soft-tissue mass. This has been of some value in further determining the nature of a mass lesion. In instances where a soft-tissue mass extends beyond the area of calcification, the changes are very suspicious of malignancy, whereas when no mass is shown beyond the wall of the lesion, the entity is more likely to be benign, particularly if the contents of the mass are fluid in nature (Weyman et al, 1982). In this instance the presence of a soft-tissue mass outside the area of calcification (Fig. 6) would, erroneously, have placed this lesion into that group suspicious of malignancy. The fluid-filled nature of the calcified cyst was not detected at CT, presumably due to the partial-volume effect. Ultrasound also failed to detect the fluid, the calcific wall casting an acoustic shadow precluding delineation of the fluid nature of the cyst.

In this patient, the uroradiological changes described all have features of renal malignancy, making exclusion of this diagnosis difficult, if not impossible. In the appropriate clinical situation, however, consideration should be given to the diagnosis of post-traumatic haematoma. Surgery, which we still consider mandatory in similar cases, may be confined to that which is necessary to confirm the diagnosis. An unnecessary nephrectomy may, thus, be avoided.

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Detection of *Toxocara* by computed tomography

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A 30-year-old patient presenting with pain and fever was shown to have an abnormal liver parenchymal pattern on both ultrasound and CT, the changes of which suggested a malignant process. The appearance, however, was later shown to be due to infestation with *Toxocara,* an appearance which has not been reported previously.

Case Report

The patient, a 30-year-old electrician, was admitted to hospital because of right hypochondrial pain and fever. This had been present for 2 weeks and, in addition, he had lost approximately 4 kg in weight. There was no relevant past history and, in particular, he did not keep any pets and had not travelled abroad. On examination an erythematous rash was noted on his thighs and the liver was found to be enlarged and tender. The blood film showed a high leucocyte count with relative eosinophilia and elevation of the liver enzymes with a normal bilirubin. Hepatitis titres were negative.

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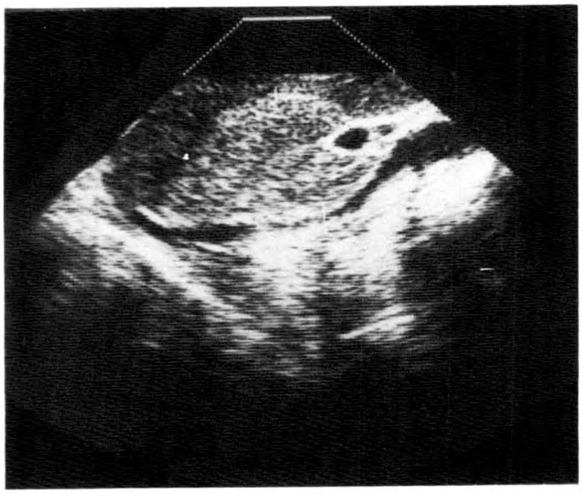

FIG. 1.

Longitudinal sonogram showing the echogenic area anterior to the inferior vena cava.

Ultrasound examination confirmed the hepatomegaly and demonstrated a large echogenic area in the centre of the liver which was displacing and compressing the inferior vena cava (Fig. 1). There was no evidence of a lucent halo around this lesion. Computed tomography before contrast medium administration (Fig. 2A) confirmed the ultrasound abnormality with a lucent area in the middle of the liver, together with a similar but smaller area in the posterior aspect of the right lobe. Following injection of contrast medium these lucent areas remained of a similar density, while there was enhancement of the surrounding liver parenchyma. In addition, two smaller, round lucencies were noted anteriorly in the liver (Fig. 2B). The outlines of these were distinct and none of the liver lesions demonstrated contrast enhancement around their margins. Ultrasound-guided biopsy was then performed and the histological appearance was that of eosinophilic infiltration in the region of the porta hepatis without any evidence of malignancy. Visceral larva migrans serodiagnosis was positive, as were the indirect fluorescent antibodies. The patient made a spontaneous recovery and was fully fit within 2 months of the original presentation. Follow-up CT and ultrasound studies confirmed resolution of the liver lesions and by the fourth month were both normal while, at the same time, the eosinophilia had decreased.

DISCUSSION

Infestation with *Toxocara* in humans usually results from the larva being transmitted through a family pet, typically a dog (*Toxocara canis*). In England and Wales the incidence is 2% with 16 000 new cases presenting per annum (Bewley, 1985). Children are more often affected than adults. The most frequent clinical signs are fever, cough, skin rashes and tenderness in the upper abdomen due to hepatomegaly. The blood film demonstrates eosinophila and the diagnosis is usually made on immunological studies. Liver biopsy, if performed, will demonstrate eosinophilic infiltration with granulomatous reactions. The larva itself is only rarely seen. There have been no previous reports in the literature describing the CT findings in larva migrans syndrome. The present case demonstrates hypodense areas in the liver on CT which persist after contrast has been administered. The appearance could easily be confused with a multifocal tumour or metastatic disease. The need to be aware of this entity is stressed, particularly in a patient presenting with fever and hepatomegaly.

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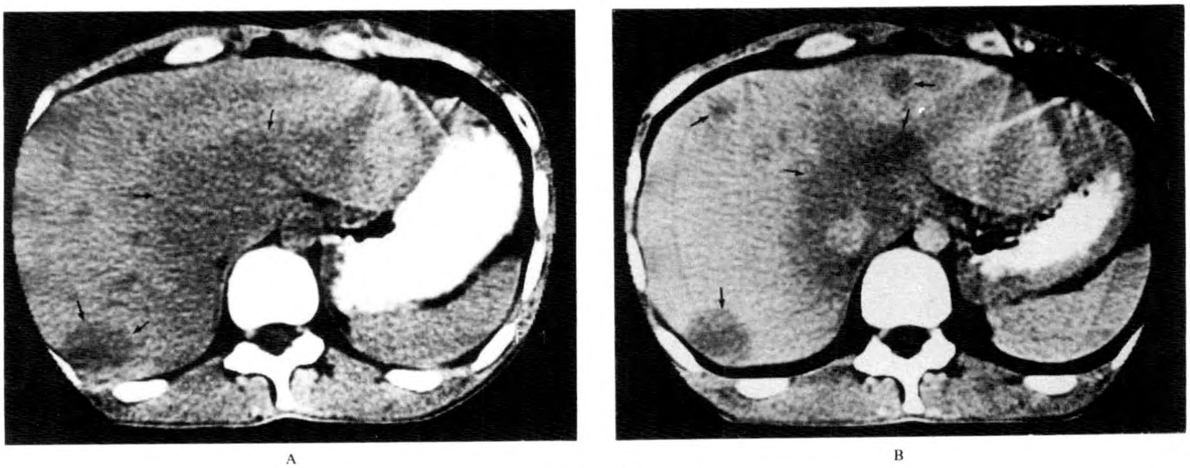

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FIG. 2.

(A) Computed tomography scan without contrast medium reveals areas of low attenuation (arrows). (B) Post-contrast scan at the same level shows inhomogeneous enhancement of liver with several areas of low density (arrows).

Book review

Obstructive Uropathy Ed. by P H. O'Reilly, pp xii + 325, 1986 (Springer Verlag, Berlin, Heidelberg, New York, Tokyo), DM 298/approx £81.50.
ISBN 3–540–15509–0
0–387–15509–0

"It has often surprised me that in order to study the subject of obstructive uropathy, it is necessary to search through various sections of several urological, surgical and radiological textbooks rather than turn to one work on the subject." The editor's opening sentence sets the rationale and aim of this book. It is a handsome volume, of special interest to radiologists and illustrated with many radiographs and scans. The editor has gathered six contributors round him, including laboratory men and radiologists (D. Rickards and P. Davies) as well as urologists. The book is divided into two main sections. upper and lower urinary tract obstruction.

So much has happened in these parts in the last two decades that there is a great deal to cover. O'Reilly's team explain new physiology as well as new techniques. The patient is kept in view throughout. The scope of the book is very wide: everything to do with obstruction is included. There is a chapter on percutaneous surgery, and textbook descriptions of anything from ureteroceles and horseshoe kidneys to malacoplakia.

The subject is a good example of the pious though important thesis that disciplines must work together to get anywhere. Given that approach, it is odd to have surgical hubris peeping through here and there. One portentous legend to a cystogram showing a lump at the bladder base reads: "Images frequently mislead. Reported as solid bladder neoplasia. Unilateral prostatic adenoma seen at cystoscopy." Elsewhere we read about "the subjective eyeballing nature of urogram interpretation". Eyeballing images through a cystoscope is something quite different of course. To pepper this review with a little aggression in the reverse direction on page 225 we have the advice "no surgeon performing prostatic surgery at present should be without access to a uroflowmeter". How many surgeons practise this—ten per cent, five per cent?

The work strikes me as a quite excellent volume which will answer very many of the questions always posed by urinary tract obstruction. O'Reilly's men are to be congratulated!

Thomas Sherwood

1986, *The British Journal of Radiology*, *59*, 521–522 MAY 1986

Case of the month

An inevitable progression?

By David M. Hansell, M.B., M.R.C.P.

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(*Received October 1985*)

At the age of 56 years the patient, a previously healthy woman, complained of dysphagia and regurgitation. A radiograph from a barium-meal examination made at that time is shown (Fig. 1), and she was treated surgically. Seventeen years later, now aged 73 years, she returned with an 8-month history of increasingly painful dysphagia and weight loss.

On examination she appeared pale and wasted, but had no lymphadenopathy or other abnormal physical signs. A full blood count and chest radiograph were normal. A barium swallow was performed and is shown (Fig. 2).

She then received treatment, following which another barium examination was performed (Fig. 3).

She improved symptomatically but developed a cough with purulent sputum. After a chest radiograph the barium-meal examination was repeated (Fig. 4).

What was the original diagnosis and treatment and what occurred 17 years later? How inevitable is this sequence of events?

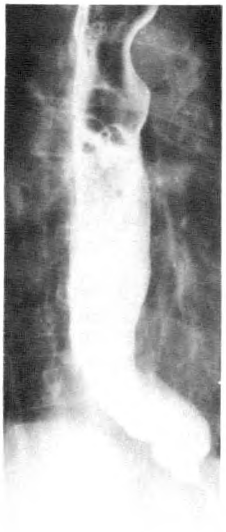

FIG. 1.

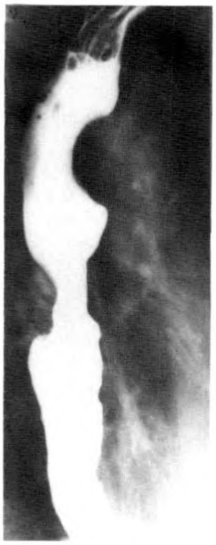

FIG. 2.

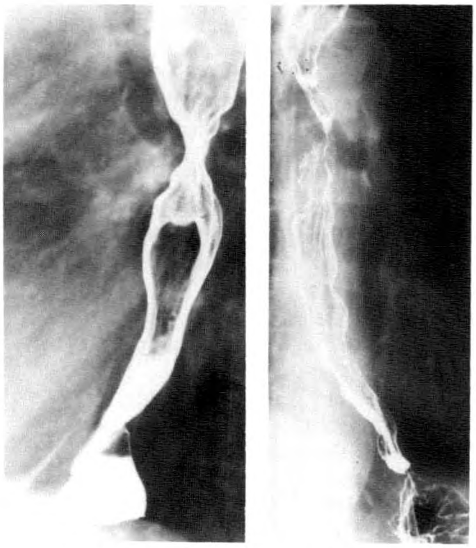

FIG. 3A. FIG. 3B.

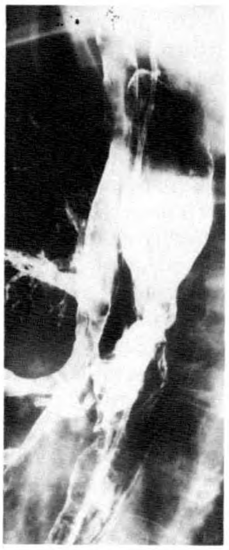

FIG. 4.

FIG. 1. Barium-swallow radiograph at first presentation. FIG. 2. Barium-swallow study at second presentation, 17 years later. FIG. 3 (A, B). Appearances after treatment. FIG. 4. Barium-swallow study after the patient developed a cough, 4 months after treatment.

Figure 1 shows a tapering lower end of a dilated oesophagus with a short, narrowed segment below the diaphragm (typical of achalasia). This was successfully treated by a Heller's myotomy.

Figure 2 shows a short, eccentrically narrowed segment of oesophagus with irregular margins and a sharp transition to normal width: the radiological signs of a carcinoma. Endoscopy and biopsy showed a poorly differentiated squamous-cell carcinoma and over the next 7 weeks she was treated with radical radiotherapy. A three-field planned technique was used with daily fractions of 200 cGy. The total effective tumour dose was 5400 cGy in 27 fractions.

After radiotherapy (Fig. 3A) there is a narrowed segment with a gradual transition to normal width. In Fig. 3B, (ulceration has now occurred) and in Fig. 4 perforation into the bronchus is shown. An Atkinson tube was inserted endoscopically, but the patient died soon afterwards, 7 months after the diagnosis of carcinoma of the oesophagus was made.

DISCUSSION

The differential diagnosis of dysphagia occurring in a patient known to have had achalasia is largely dependent upon the time interval between the diagnosis of achalasia and the recurrence of dysphagia. Reflux oesophagitis with consequent stricture formation occurs in up to 52% of patients following myotomy, usually within 4 years, and many surgeons combine a Heller's myotomy with an anti-reflux procedure to prevent this (Black et al, 1976). The typical post-myotomy appearances of the lower oesophagus are clearly seen in Fig. 3A where a fluid level is present within the mucosal herniation. This is often visible in only one projection.

The differential diagnosis of dysphagia in an elderly patient is between carcinoma, stricture, neuromuscular and "other" causes. Pseudobulbar palsy and myasthenia gravis manifest themselves as widespread neurological disturbances and are almost exclusively confined to abnormalities of initiation of swallowing and upper oesophageal function. Virtually all patients with Parkinson's disease have abnormal oesophageal motility disorder on cineradiography and up to 20% complain of dysphagia. Other causes of dysphagia in this age group are scleroderma, the Plummer–Vinson syndrome and extrinsic compression caused by mediastinal lymph nodes or an aortic aneurysm, usually readily identifiable on barium-swallow studies.

The history of this patient and the recognised association between achalasia and oesophageal carcinoma make malignant change the most likely cause of dysphagia. The reported incidence of squamous-cell carcinoma in patients with achalasia varies between 1.7% and 29% (Wychulis et al, 1971). The treatment of achalasia does not appear to reduce the risk of subsequent development of carcinoma of the oesophagus. The carcinoma is often at the site of the fluid level seen in the oesophagus prior to treatment. The prognosis of patients with achalasia who develop carcinoma is particularly poor since the tumour will have reached a considerable size before obstruction occurs. In addition, early detection by endoscopy or barium swallow may be hindered by the presence of fluid or food residue in the oesophagus.

The association between achalasia and oesophageal carcinoma has recently been questioned (Chuong et al, 1984) A group of 91 patients with achalasia were followed up for periods ranging from 6 months to 23 years. None of these patients developed oesophageal carcinoma. In another part of the study there was no convincing history of previous achalasia in 153 patients with oesophageal carcinoma. It is likely that oesophageal carcinoma is an extremely rare complication of achalasia and there is no justification for repeated barium-swallow studies or endoscopies to detect early carcinoma.

Some patients with the typical radiological features of achalasia may have a carcinoma of the oesophagogastric junction (Ott et al, 1979) and this should be suspected in any patient over 40 years old with recent onset of oesophageal symptoms and the radiological signs of achalasia.

The complication of tracheo-oesophageal fistula is more commonly seen as a result of a primary bronchogenic carcinoma invading the oesophagus. Because of the relative mobility of the oesophagus, a carcinoma of the oesophagus is more likely to spread along the submucosa than to involve the surrounding mediastinal structures. The treatment with radical radiotherapy almost certainly contributed to the formation of the fistula in this case. It is important to perform a barium-swallow examination with the patient prone if a tracheo-oesophageal fistula is suspected.

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1986, *The British Journal of Radiology*, 59, 523–525

MAY 1986

Short communications

Radiotherapy employing three fractions in each day over a continuous period of 12 days

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(*Received October 1985 and in revised form December 1985*)

During recent years schemes of radiotherapy incorporating multiple treatments in one day have been introduced into the clinic. These can lead to a reduction in the overall duration of treatment (accelerated fractionation), an increase in the number of fractions in the same overall time (hyperfractionation), or a combination of both (Fowler, 1984).

Two to five treatments have been given each day from Monday to Friday for 1, 2 or more weeks (Svoboda, 1978; Van der Schueren et al, 1985; Wang, 1985). It has usually been found necessary to reduce the individual dose increment from the conventional 1.8–2 Gy to between 1 Gy and 1.6 Gy but, even then, immediate reactions have prevented most workers from achieving a satisfactory total dose without interruption. Commonly, a split-course technique is employed with a rest period of 2–4 weeks to allow normal tissue reactions to settle before further radiotherapy is given. Retrospective comparisons in head and neck cancer have given improved results (Wang, 1985) but randomly controlled trials have not, so far, given convincing support (Van der Schueren et al, 1985).

Part of the benefit of accelerated fractionation should result from a reduction in time for regrowth between fractions. This is believed to be particularly important in tumours with a high rate of proliferation (Fowler, 1984). However, the pause in treatment at a weekend and the long gaps which may occur when a split-course technique is employed, must allow a regrowth of tumour, thus undermining this justification for accelerated fractionation. In none of the studies so far reported involving multiple treatments in 1 day has treatment been extended into the weekend period, although reports have been made where, with daily fractionation, the treatment has continued through Saturday and Sunday (Lipsett et al, 1984). We decided to combine hyperfractionation and accelerated fractionation and, in order to gain the greatest benefit, the period of treatment has been planned to be continuous with all gaps and rest periods avoided.

When considering the number and distribution of treatments in 1 day we must allow for recovery of sublethal injury to normal cells after each fractionation. The intervals between fractions should not be shorter than 3 h and should, if possible, be greater than 4 h (Thames, 1984). Repair is almost complete at 6 h so there is probably little further advantage to be achieved by increasing to 8 h (Fowler, 1984).

METHOD

Thirty-six fractions have been given over a continuous period of 12 days with a 6 h gap between the first and second and between the second and third treatments of each day. The course was begun on a Monday morning and the patients were treated between 8.00 and 9.00 a.m.; 2.00 and 3.00 p.m.; 8.00 and 9.00 p.m. Thus, the first and last treatments of the day were given outside normal working hours and only the middle fraction given within the normal working day.

Treatment was continued through one weekend with the same timing as on the weekdays. The final, 36th, treatment, was given on the evening of the second Friday. In this way only one weekend was involved. Only 10 of 36 treatments were given within normal working hours but radiographers and physics staff readily volunteered to carry out the extra duties required. On each occasion when treatment was given, two radiographers and one physics technician were present and a consultant or registrar was available or within 5 minutes' call. A 5 MV linear accelerator was available for all treatments. Machine failure did not occur but, as a precaution, alternative arrangements were made for treatment to be given on another accelerator. It was necessary to admit all these patients to hospital for the full 12-day period in order that they should be easily available for each treatment. In some cases conventional treatment could have been given on an outpatient basis, but others, because of extensive disease, impaired general condition due to coincidental disease or because their home was at a distance from the treatment centre, would have required admission even for conventional management.

A minimum tumour dose of 1.4 Gy was given in each of the 36 fractions so as to give a total dose of 50.4 Gy, a dose felt to be a satisfactory one which might be associated with a high level of local tumour control.

In a series of three treatment periods, 11 patients—seven with inoperable bronchial carcinoma and four with advanced head and neck tumours—were included (Table I). In all cases, large and small treatment volumes were planned, the former included all known tumour with probable and possible areas of spread and the latter included sites of known tumour only. In the patients with advanced head and neck tumours the large volume invariably encompassed the whole neck and most of the oral cavity and pharynx; in the patients with bronchial carcinoma, the whole mediastinum, as well as areas of lung, were included. Lung volumes were deduced from computed tomography (CT) images and a correction factor of 0.3 employed in calculation of the dose distribution. The large volume was given a minimum tumour dose of 42 Gy in 30 fractions over 10 days, the final six fractions being given to the reduced volume to achieve a total dose of 50.4 Gy and in 10 of 11 cases it was possible to exclude the spinal cord in this phase of treatment.

IMMEDIATE TOLERANCE

A marked early reaction in normal mucosa in the head and neck region and in the oesophagus was predicted from radiobiological considerations which also suggested that this would not be matched by any increase in late changes (Fowler,

TABLE I

DETAILS OF PATIENTS AND TREATMENT RESPONSE

Case	Sex	Age (years)	Primary site	TNM staging	Histology	Date of first treatment	Local tumour response	Status
1	M	50	Bronchus	$T_3N_2M_0$	Poorly differentiated squamous-cell carcinoma	7.1.85	Apparent complete regression	Well at 10 months
2	M	60	Bronchus	$T_1N_2M_0$	Undifferentiated carcinoma	7 1 85	Apparent complete regression	Well at 10 months
3	M	53	Bronchus	$T_3N_2M_0$	Poorly differentiated squamous-cell carcinoma	7.1.85	Apparent complete regression	Well at 10 months, metastases in R arm
4	M	55	Tonsil	$T_3N_0M_0$	Moderately differentiated squamous-cell carcinoma	7.1.85	Complete regression	Well at 10 months
5	F	68	Bronchus	$T_3N_2M_0$	Poorly differentiated squamous-cell carcinoma	13 5.85	80% regression before tumour hidden by fibrosis	Hepatic metastases at 4 months
6	F	65	Bronchus	$T_3N_3M_0$	Poorly differentiated carcinoma	13.5.85	Apparent complete regression	Well at 5 months
7	M	70	Bronchus	$T_3N_0M_0$	Poorly differentiated carcinoma	13.5.85	80% regression	Died of congestive heart failure at 4 months
8	M	74	Oropharynx	$T_4N_2M_0$	Poorly differentiated squamous-cell carcinoma	13.5.85	Complete regression of primary; some residual adenopathy	Well at 5 months
9	M	73	Tongue	$T_3N_0M_0$	Moderately differentiated squamous-cell carcinoma	24 6 85	Complete regression	Well at 3 months
10	M	69	Tonsil	$T_2N_3M_0$	Well differentiated squamous-cell carcinoma	24 6.85	Complete regression	Well at 3 months
11	M	73	Bronchus	$T_2N_0M_0$	Poorly differentiated squamous-cell carcinoma	24 6 85	Complete regression seen at post-mortem examination	Died at 1 month, myocardial infarct

1984) Mucosal reactions became troublesome in all cases However, six of the seven patients with bronchial carcinoma were discharged home soon after completion of their treatment. Although they were restricted to a liquid diet for 2 weeks, they did not require readmission for special care. The seventh patient was readmitted for a further 2 weeks while the reaction subsided, but oesophageal intubation was not found necessary. All four patients with head and neck cancer were kept in hospital for a minimum of 2 weeks after completion of treatment. They developed a membranous reaction throughout the area irradiated, but none required tube feeding to overcome it In all cases swallowing was normal or near normal within 4 weeks of the completion of radiotherapy

LATE REACTIONS

It is too early to give meaningful data concerning late changes due to this scheme of radiotherapy. The first group of patients is now 10 months from completion of treatment and show no adverse normal tissue reactions except for radiation fibrosis in lung and this follows a pattern to be expected when therapeutic doses of radiation are used in the management of bronchial carcinoma. It is noteworthy that, in all four patients with head and neck tumours, where both parotid glands were included in the field of radiotherapy, dryness of the mouth has been a minor problem.

TUMOUR RESPONSES

All patients have been carefully monitored to determine tumour control Those patients with bronchial carcinomas have, in addition to careful clinical examination, undergone monthly chest radiography and at 2-monthly intervals planar tomography and CT have been performed.

The primary tumour has been observed to regress entirely and full healing to take place in all four patients with head and neck tumours. In two of these patients there were extensive deposits in the nodes in the neck, one has shown complete regression but, in the other, some residual adenopathy remains at 3 months, although this continues to regress.

Of the seven patients with bronchial carcinoma, five have shown an apparent complete regression of tumour. In four this has been assessed by radiological techniques while in the fifth, who died due to a myocardial infarct, histological study of post-mortem material failed to show any residual tumour in the primary site. In the remaining two patients the tumour regressed by more than 80% One of these patients succumbed to longstanding cardiac disease and a post-mortem examination was refused. In the other, radiation fibrosis has now obscured the primary site and the completeness of regression cannot be determined radiologically

DISCUSSION

In this pilot study of multiple treatments in 1 day given over a continuous period of 12 days, the technique has proved to be a practical one. Immediate reactions have not been unduly troublesome and tumour responses have been encouraging. Five of seven patients with advanced bronchial carcinoma have shown evidence for complete regression and this compares favourably with only seven complete regressions seen in 62 similar patients previously treated by radiotherapy

(Saunders et al, 1984). To this can be added the complete regression observed in the primary site in all four patients with advanced head and neck tumours.

The treatment regime is a promising one which is now being explored further. A fully detailed report of the patients included in this pilot study will follow.

ACKNOWLEDGMENTS

We wish to thank Professor J. F. Fowler and Dr Julie Denekamp for their helpful advice and support. This work would not have been possible without the enthusiastic co-operation of our radiographers and physics staff. Sister Cheryl Des Rochers and Dr Eamonn Dunphy have given considerable help in the follow-up care of the patients. We are grateful to our colleagues in Chest Medicine and Surgery, ENT Surgery and Radiotherapy and Oncology who have referred patients to us for inclusion. We wish to thank Mrs Eileen Davies for the preparation of the manuscript. The continued support of the Medical Research Council and the Cancer Research Campaign is gratefully acknowledged.

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Early experience with combined interstitial hyperthermia and brachytherapy

By P. R. C. Dunlop, F.R.C.R., R. J. Dickinson, Ph.D., J. W. Hand, Ph.D., *A. J. Munro, M.R.C.P., F.R.C.R. and *K. A. Vallis, M.R.C.P.

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Obtaining benefit from the use of hyperthermia in treating cancer is strongly dependent on the success of the heat treatment in raising the temperature adequately throughout a tumour volume (Dewhirst & Sim, 1984). Interstitial hyperthermia offers one of the best methods of uniform heat delivery (Doss & McCabe, 1976). The radiofrequency (RF) system described here is relatively simple and integrates well with interstitial brachytherapy treatment using afterloaded iridium-192 wires.

METHOD

Under general anaesthesia, hollow stainless steel needles (1.8 mm o.d.) are implanted into the tumour using a central trochar. The desired arrangement of needles is two parallel planes of equal length, evenly spaced, with 1 cm between planes and between needles. Perspex strips or plastic tubing with pre-cut holes are used as jigs to ensure appropriate geometric arrangement, since unacceptable overheating will occur wherever two adjacent needles converge. The surrounding normal tissues and the skin at the entry and exit points are electrically insulated with short lengths of Teflon sleeving. Sometimes, the size or shape of a lesion only allows the insertion of a single plane of needles, in which case an overlying copper-foil disc, with saline-soaked gauze and electrocardiography gel to facilitate good electrical contact, can be used as the second electrode, although this arrangement produces less satisfactory heat distribution than the two-plane implant.

Radiofrequency power (20–50 W) at 500 kHz is applied to the two planes of needles, heating all the tissue in between (Figs 1, 2). A plug-in distribution matrix allows flexible connection of the implanted needles to the power source. A 1 : 1 isolation transformer is inserted into the circuit as an electrical safety precaution. Forward and reflected power are monitored during treatment.

Multijunction manganin–constantan thermocouples, sheathed in nylon tubing (0.63 mm o.d.), are passed along separate 18-gauge catheters positioned midway between the planes of the implant to record temperatures within the tumour. Data from 30 thermocouple channels are rapidly handled to provide comprehensive thermometry, which is essential to any hyperthermia technique. Two heat sessions are usually given: the first, soon after implantation and the second, 3 or 4 days later, after completion of the irradiation. This allows any resistance (or thermotolerance) that may have been induced by the first hyperthermia treatment to decay (Overgaard, 1982).

The prescribed radiation dose (normally 20–40 Gy at 1 cm

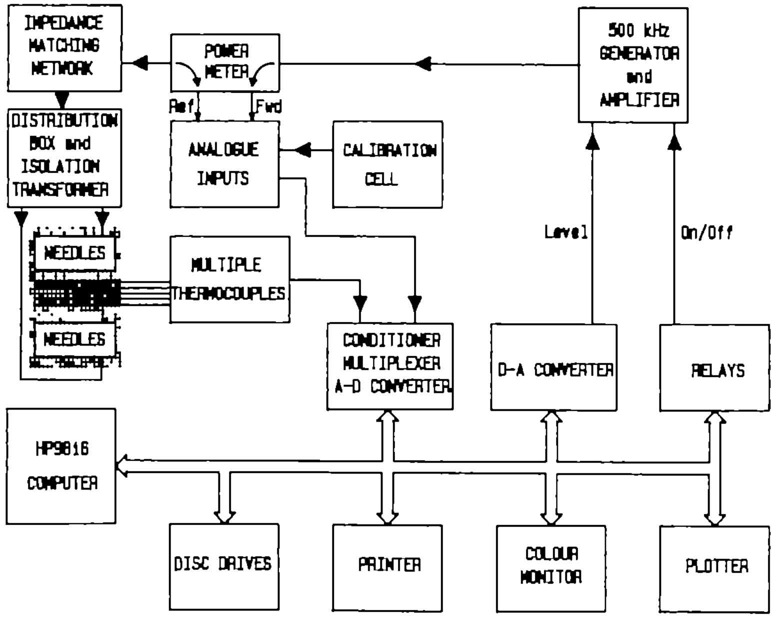

FIG. 1

Block diagram of the RF interstitial system.

from each plane) is delivered by iridium wires which are passed down each hollow needle when the patient has returned to the ward. The entire implant is removed after completion of the second heat session.

Hyperthermia treatments are assessed in real time, using the concept of "thermal dose", measured as the equivalent time of heating at 43°C (Sapareto & Dewey, 1984). Needles adjacent to well heated regions which reach satisfactory thermal doses first are disconnected to concentrate power on cooler regions.

CLINICAL RESULTS

Nine patients with bulky recurrent tumours at various sites have been treated with a combination of interstitial iridium brachytherapy and hyperthermia (Table I). All but one tumour had been irradiated previously. Nine out of 16 hyperthermia treatments reached a minimally satisfactory "dose" of at least 20 min equivalent heating at 43°C at all measured points within the tumour volume. Patient intolerance (due to poor skin insulation or converging needles) limited the power that could be applied and resulted in inadequate dose accumulation in the remaining seven treatments.

All patients had been selected for interstitial brachytherapy and the additional hyperthermia added little inconvenience or discomfort. Conductive needles are required to carry the RF current and these rigid needles are marginally less comfortable than the alternative flexible Teflon catheters, used in standard implantation techniques (Paine, 1972). The maximum follow-up period in this group of patients is 6 months, too early to analyse data in terms of tumour response, and there is insufficient information to correlate the relative contributions

TABLE I

PATIENTS TREATED BY RF INTERSTITIAL HYPERTHERMIA AND RADIATION

No.	Tumour			Implant	Mode	Radiation dose (Gy at 1 cm)	Outcome
	Type	Site	Size (cm)				
1	Breast	Axilla	6.5 × 7.5	2-plane	▼-RT-▼	20	Good PR
2	Breast	Chest	8 × 12	1-plane	▽-RT-▽	20	NR; static
3	Breast	Chest	8.5 × 9	2-plane	▼-RT-▽	40	Good PR
4	Squamous (pinna)	Neck	3 × 3.3	1-plane	▽-RT-▽	15	NR
5	Breast	Chest	4 × 5	1-plane	▽-RT	60	PR
6	Squamous (pyriform fossa)	Neck	3 × 3.5	1-plane	▼-RT-▼	40	PR
7	Residual 1°	Breast	6 × 8	2-plane	▼-RT-▼	25	Some reduction in size at 1 month
8	Fibrosarcoma recurrent 1°	Thigh	5 × 8	2-plane	RT-▼	20	NR
9	Breast	Chest	6 × 10	2-plane	▽-RT-▼	40	Reduction in size at 2 months

RT = radiotherapy, ▼ = hyperthermia session with a minimum of ≥ 20 min Eq 43°C, ▽ = hyperthermia session with a minimum < 20 min Eq 43°C, PR = partial response, NR = no response.

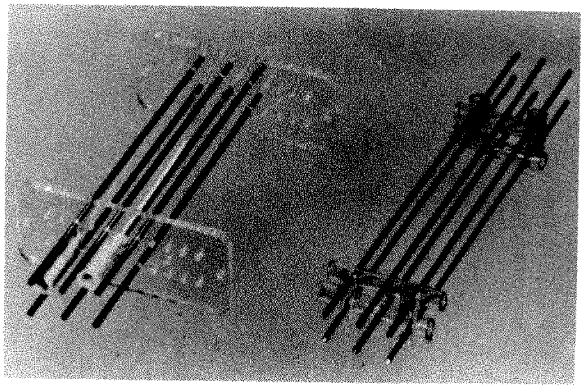

FIG. 2.

Photograph of needle arrangement, showing two planes held in parallel geometry by either rigid perspex or soft plastic jigs.

of hyperthermia and radiation to tumour control. However, substantial regression and useful palliation were obtained in four patients, with some reduction in tumour volume in two others so far. It is the impression of the authors that the best responses were associated with the most satisfactory heating patterns.

DISCUSSION

Interstitial hyperthermia has the advantage of being capable of delivering uniform heating to large tumour volumes, while sparing the surrounding normal tissues. It is safe and easily combined with interstitial radiation therapy with minimal additional discomfort. The combination of hyperthermia and conventional irradiation might well prove advantageous in terms of therapeutic ratio for tumour control and the results from other published series (for example, Manning et al, 1982; Cosset et al, 1985) are encouraging. A multichannel system with individual control of power to chosen groups of needles is under development and should permit more uniform heat delivery. A trial in which patients with bulky accessible tumours are randomly allocated to either interstitial irradiation alone or interstitial irradiation and hyperthermia is now being considered.

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Book review

Paediatric Neurosonography: Clinical, Tomographic and Neuropathological Correlates. By Asma Qureshi Fischer, Joseph C. Anderson, Robert M. Shuman and Warren Stinson, pp 267, 1985 (John Wiley & Sons, New York), £46.00
ISBN 0-471-89252-1

The aim of this excellent book is to act both as a teaching manual for neurosonography and as a reference text. In taking the form of an atlas it provides reproductions of ultrasound images of a high standard, accompanied by a concise but clear description and a brief clinical history. In conjunction with the ultrasound scans, the authors have illustrated pathological specimens which greatly assist in interpretation. The photography of the specimens is not quite of the same high standard as the ultrasound images, but this does not seriously detract from the clarity with which the information is presented

The early chapters comprehensively cover ultrasound technique and normal anatomy; of particular value is the detailed description of the change in appearance of the neonatal brain with maturation. The remaining chapters describe most of the pathological conditions encountered in the neonatal period; classical complications of prematurity and hypoxia are well covered, but the section on congenital malformations is rather short for a reference text.

The book is recommended to anyone wishing to learn paediatric neurosonography. It will be of value in paediatric neonatal units particularly as a reference book for normal anatomical variation and for the recognition of most pathological conditions

Juliet Britton

1986, *The British Journal of Radiology*, 59, 529–530 MAY 1986

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

Dosimetry of the neutron beams at Hammersmith and Edinburgh

THE EDITOR—SIR,

In 1976 we wrote to report a revision of neutron dosimetry at Hammersmith (Parnell & Bewley, 1976). The effect of this was that the old standard dose of 1440 rad (cGy) was changed by 8% and became 1560 rad (cGy). Dosimetry at Edinburgh was based on the new Hammersmith values.

Since 1976, various protocols for neutron dosimetry have been published It is now customary in Europe to use the European Protocol (Broerse et al, 1981). In this protocol the various factors which are used in neutron dosimetry were assigned rather different values from those previously used at Hammersmith and Edinburgh. When dosimetric measurements were made using the new protocol, the values of neutron dose, D_N, turned out to be greater than the value used for clinical work at Edinburgh by 3–4% and at Hammersmith by 5–6%. Thus, the standard neutron dose at Hammersmith would be about 1645 cGy instead of 1560 rad. For the sake of continuity, however, the old values continued to be used for the treatment of patients. The decision to do this was reinforced by the knowledge that neutron therapy at both centres would be closing in 1985.

In addition, most neutron therapy centres specify the total dose rather than the partial dose of neutrons alone. The proportion of the total dose which is due to gamma rays varies with depth, field size and beam filtration. For most treatments given at Hammersmith the proportion was between 5% and 8%. If 7% is taken as a representative figure, the standard total dose at Hammersmith becomes 1760 cGy.

Recently, a comparison of the randomised trials of fast neutrons for the treatment of cancer of the mouth and throat at Edinburgh and Hammersmith has been made (Medical Research Council, 1986). As a part of this investigation, a dosimetric intercomparison was made between the two centres in order to assess the value of the neutron doses given to the patients. This showed that the clinical dosimetry at the two centres was identical within 1%.

This close accord may seem strange in view of the 2% difference when dose was measured using the protocol. This difference seems to be due partly to calibration with ^{137}Cs γ rays at Hammersmith and 4 MV X rays at Edinburgh and partly to small differences between the responses of the chambers to the neutron beams. The latter effect may be due to small differences in the composition of the A-150 plastic used in the various chambers. The close accord of the clinical doses is to be expected as the dosimetry at Edinburgh was originally based on the methods used at Hammersmith.

The results of the clinical trials in Edinburgh have recently been prepared for publication. In each report the dose is given in terms of the total dose including the gamma contribution. These doses have not been updated and are, therefore, about 3% lower than would have been measured using the European protocol.

As the European protocol is now in general use on this side of the Atlantic, any estimates of the clinical RBE of neutron beams relative to Hammersmith must take into account that the nominal dose of 1560 rad is really 1645 cGy of neutrons or about 1760 cGy of total dose.

Yours, etc.,
D. K. BEWLEY
C. J PARNELL
*J. R. WILLIAMS

MRC Cyclotron Unit, Hammersmith Hospital,
Du Cane Road, London W12 0HS and
*West of Scotland Health Boards,
Department of Clinical Physics and Bio-engineering,
11 West Graham Street,
Glasgow G4 9LF

(*Received January 1986*)

REFERENCES

BROERSE, J. J, MIJNHEER, B. J. & WILLIAMS, J. R., 1981. European protocol for neutron dosimetry for external beam therapy. *British Journal of Radiology*, *54*, 882–898

PARNELL, C. J. & BEWLEY, D. K., 1976. Dosimetry of the fast neutron beam produced by the MRC cyclotron. *British Journal of Radiology*, *49*, 298.

MEDICAL RESEARCH COUNCIL, 1986. A comparative review of the Hammersmith and Edinburgh neutron therapy trials of certain cancers of the oral cavity, oropharynx, larynx and hypopharynx. *British Journal of Radiology*, *59*, 429–440.

Diagnostic radiological examinations of women of reproductive capacity

THE EDITOR—SIR,

The BJR Editorial (Anonymous, 1986) on this subject has cited the advice given by the Royal College of Radiologists in their Newsletter. This reads in part: "If a woman is pregnant or considers she may be pregnant then direct irradiation to the abdomen and pelvis should be avoided" This paraphrases the advice given by the National Radiological Protection Board (1985), but omits the National Radiological Protection Board's definition of pregnancy used in this context. This is: "It would be prudent for referring physicians and radiologists to treat as pregnant any woman ... when a period is known to be overdue or clearly missed" There need be no special limitation on pelvic or abdominal radiography until a period is due or overdue. This is the advice of both the National Radiological Protection Board and the International Commission on Radiological Protection.

Yours, etc.,
J. G. B. RUSSELL

Department of Radiology,
St Mary's Hospital,
Whitworth Park,
Manchester 13

(*Received February 1986*)

REFERENCES

ANONYMOUS, 1986. Editorial. Diagnostic radiological examinations of women of reproductive capacity *British Journal of Radiology*, *59*, 1–20.

National Radiological Protection Board, 1985. *Exposure to Ionizing Radiation of Pregnant Women: Advice on the Diagnostic Exposure of Women Who Are, or Who May Be Pregnant*. ASP 8 (NRPB, Harwell)

TRAPNELL, D. H., 1983. Design, dynamics and deduction: a radiologist looks at the human lung *Clinical Radiology, 34,* 479–490

Bleomycin lung: computed tomographic observations

THE EDITOR—SIR,

I read with interest the article by Rimmer et al (1985) on the above subject.

The observation of definite tendencies for posterior distribution of the changes in bleomycin lungs is very interesting indeed. I would like to suggest that the perfusion of the lungs may play an important role in the distribution of these changes. Bleomycin reaches the lungs mainly via the bloodstream, therefore the areas which are well perfused could be more susceptible to damage in comparison with the areas which are poorly perfused. I presume that during the administration of bleomycin the patient is lying in a supine position. This makes the posterior part of the lung better perfused in comparison with the anterior part, due to the effect of gravity. I think a knowledge of the position of these patients during the administration of the bleomycin, and in the period immediately after administration, would be very helpful.

The inconsistency of this observation could be explained by the fact that some patients may have an abnormal perfusion pattern of the lungs due to obstructive airways disease or other causes. In obstructive airways disease, the areas which are poorly ventilated will also be poorly perfused (Trapnell, 1983). I expect in these patients the changes secondary to bleomycin may be confined only to the areas of normal perfusion.

Assessing the perfusion of the lungs before commencing bleomycin therapy, using isotope lung scans, could be very useful It will be interesting to see whether or not the distribution of bleomycin damage will include areas of poor perfusion.

Yours, etc.,
S. K. MORCOS

Department of Radiology,
Lodge Moor Hospital,
Sheffield S10 4LH
(*Received November 1985*)

REFERENCES

RIMMER, M. J., DIXON, A. K., FLOWER, C. D. R. & SIKORA, K., 1985. Bleomycin lung: computed tomographic observations. *British Journal of Radiology, 58,* 1041–1045.

(*Authors' reply*)

THE EDITOR—SIR,

The posterior distribution of changes of bleomycin lung cannot be explained by the patient's position. Bleomycin was given in nearly all patients when they were sitting up in a chair, in the outpatient clinic or on the ward; very rarely are the patients supine

The patients in our series were all young men with no previous respiratory problem and they had no evidence of chronic obstructive airways disease.

Yours, etc.,
M. J RIMMER
A. K. DIXON
C. D. R. FLOWER
K. SIKORA

Addenbrooke's Hospital,
Hills Road,
Cambridge CB2 2QQ
(*Received December 1985*)

Phrygian cap updated?

THE EDITOR—SIR,

In the paper by Williams et al (1986), I was interested to see an illustration depicting a Phrygian cap. Perhaps, in this age of television, the term "Smurf's cap" might be a more recognisable and meaningful description to radiologists in training, especially those with young children!

Yours, etc.,
S. HAMILTON

Department of Radiology,
Meath Hospital,
Dublin 8
(*Received February 1986*)

REFERENCE

WILLIAMS, I., SLAVIN, G., COX, A., SIMPSON, P. & DE LACEY, G., 1986. Diverticular disease (adenomyomatosis) of the gallbladder: a radiological–pathological survey. *British Journal of Radiology, 59,* 29–34

Obituary

C. N. Rocky—1903–1986

Charles Rocky died peacefully in January 1986 following a short period of failing health. He was a long-standing member of the British Institute of Radiology and, before that, of the Rontgen Society, which he joined in 1924, introduced by his father, Mr H. Rocky, then Managing Director of "G.R.S.A.", suppliers of X-ray and surgical equipment.

Mr C. N. Rocky trained for several years in Europe, returning to England in 1928 to take up the post of Chief Engineer—in the firm his father had founded. A few years later Mr H. Rocky contracted a serious illness and Charles Rocky undertook management. He quickly gained the respect of his engineers and supporting staff, showing a rare ability to delegate responsibility. In those days, co-operation between equipment makers and radiologists was an active spur to technical development. When the writer joined "G.R.S.A." in 1928, the induction coil and gas-tube were still used. The high-tension transformer and hot-cathode tubes were making headway, though handicapped by the prevailing direct-current mains supply which necessitated the installation of rotary converters to provide the alternating current which transformers required. Rectification of tube current was carried out by mechanical means, later superseded by hot-cathode valves. Connection to the X-ray tube was still via open leads carried on suitable insulators. Not until the early 1930s did shock-proof shielding of the tube become available, soon to be followed by full shock-proofing for the entire installation. These changes entailed new thinking on the part of manufacturers, service engineers and equipment users. Committees were formed to promote radiation and electrical safety and Mr Rocky was much in demand for his technical experience and measured common sense. In 1939 came the problems of war effort by the British X-ray industry; all makers had to increase their output and, under the direction of Mr Rocky, the capacity of "G.R." (as it had come to be called) was enhanced by bold additions to staff, factory space, and research and development. It was a strenuous time for all concerned and not helped by air-raids and material shortages. The Forces made their own specialised demands on the industry and "G.R." was called upon to develop Mass Chest Radiography for the Navy.

After 1945 the BIR could begin slowly to pick up the threads of its academic activities, organising congresses and exhibitions. A committee from the X-ray industry undertook responsibility for exhibition of new equipment and Mr Rocky was much involved on behalf of his firm and as a member. It seemed fitting that when H.M. The Queen opened the new premises of the BIR Mr Rocky was introduced to her as the oldest serving member of the Institute. We at "G.R." who had been involved in his work over the years felt it to be no more than his due! It is doubtful if any manager has ever engendered greater respect and loyalty among all his staff. It was a source of pride to him that a number of engineers who had trained under him were able to move on to positions of authority in other firms, Regional Boards and the Medical Officer of Health Inspectorate He was also gratified that his son and two grandsons followed him in the field of radiation physics.

Mr Rocky retired from the X-ray industry in 1968, but continued in committee work for the Institute and for the Society of X-ray Technology. He will be remembered with respect, and by us who were in daily contact with him, real affection too. Even after retirement he maintained contact with those who had so happily kept the wheels turning. To his wife and son we offer our sincere condolence.

S. H. Mathews

Library news

The BIR Library is open weekdays 9am–6pm

The Librarian, Mrs Gunnel Ingham, is in attendance Tuesdays and Thursdays 11am–4pm; Mrs Angela Lansdown, daily 9am–5pm.

The journal stock includes more than 100 titles. Though journals may not be taken out of the library, there is a photocopy service, also available by post. A list of current journals is available on request and is also published in the Bulletin twice a year.

Most books (excepting the historical collection) are available on loan.

Further information: telephone 01-580 4085.

Recent additions to the Library

Flanagan, J. J. & Maisey, M. N.: An atlas of normal skeletal scintigraphy. 1985

Martin, A. & Harbison, S. A.: An introduction to radiation protection. 2nd edit. 1979

Mould, R. F. (Ed.): Brachytherapy. 1984

University of Bristol & Bristol and Weston Health District: Procedures following major radioactive contamination. Proceedings. 1981

BSI document 6628 : 1985 IEC 806–1984: BSM for determination of the maximum symmetrical radiation field from a rotating anode X-ray tube for medical diagnosis

BIR: The second Mayneord lecture and clinical discussion. Radiology '85. VHS video tape

New journals: BMUS Bulletin
Referativnii Zhurnal. 70. Radiatsionnaya biologiya (USSR)

Press releases

Cancer Surveys

Editor: L. M. Franks
Imperial Cancer Research Fund Laboratories

The Imperial Cancer Research Fund, one of the oldest organisations in the field of cancer research, is a charity which has supported research on the causation, prevention and treatment of cancer in its own laboratories and clinical units for over 80 years. It has now begun a new project as a service to cancer research by publishing a series of "Cancer Surveys".

The purpose of "Cancer Surveys" is to provide a comprehensive review of areas in oncology and related fields in which there is current scientific or clinical interest. A major objective is to bridge the gap between the clinic, the laboratory and the epidemiologist.

Each issue of the journal is concerned with one selected topic and provides a definitive account of the present state of knowledge. The journal appears quarterly, and for each issue there are one or more guest editors with special knowledge of the field, who provide general assessments of the topics. Contributors are invited to review specific areas in which they have made important contributions, to concentrate on their own activities and interests, to include research findings which may or may not have been published elsewhere, and to relate epidemiological and laboratory research to clinical problems. The object is to have papers which are of importance not only historically, but also as the foundation of contemporary and future research, and which stand as original contributions in their own right.

With many journals publishing reports directly related to cancer, and innumerable others dealing with the enormous range of biological topics which are of interest to cancer workers, this journal is of particular importance both for clinicians and for laboratory research workers.

ICR volumes wanted

The BIR Library possesses material from most (but not all) International Congresses of Radiology, but the Institute should have *all* these books and pamphlets. The librarian would be very grateful for help to fill the gaps.

Two issues in particular may be of interest: *The Clinical Management of Solid Tumours in Childhood,* ed. by T. J. McElwain, and *Recent Advances in Treatment and Research in Lymphoma and Hodgkin's Disease,* ed. by R. T. Hoppe. Orders should be made to the Journals Subscription Dept, Oxford University Press, Walton Street, Oxford OX2 6DP.

New service offered on printed X-ray envelopes

MBF Business Forms of Nottingham have just launched a new service on printed X-ray envelopes with the following features: a diverse range of sizes and specifications to meet any particular hospital's individual requirements; a "stock"-sized envelope size 14" × 17" (*i.e.* 367 mm × 445 mm) at especially competitive prices—this being the single most popular size used throughout the Health Service; a facility to print extra large envelopes (up to size 22" × 15") for such applications as "leg" X-rays, etc.; a "storage and call off" facility to enable Health Authorities to buy in larger bulk quantities, thus saving money, whilst at the same time dramatically reducing time and administration costs, etc.

Price lists and special quotations are readily available from MBF Business Forms Ltd, 20 Rockery Rd, West Bridgford, Nottingham NG2 6BG (Tel. 0602-813786).

Medical aid and journals for Poland

Three years ago we appealed to readers to send copies of the BJR or any other medical journals they could spare to Poland. Current Western textbooks and journals are still desperately needed in Polish hospitals and medical schools. All medical equipment is in very short supply and old X-ray equipment in working order would be very much appreciated.

"Medical Aid for Poland Fund" regularly sends trucks of medical equipment; they have sent over £7M of medical aid. If any readers can help, please contact the Hon. Secretary of the Fund, Dr Joanna Zakrzewska at 54 Denbigh Street, London SW1V 2EU.

Electrotechnical, power, telecommunication, electronics, lighting and colour terms

BS 4727 *Electrotechnical, power, telecommunication, electronics, lighting and colour terms* Part 3 *Terms particular to telecommunications and electronics* Group 08 *Acoustics and electroacoustics terminology,* just published, contains terms and definitions relating to acoustics and electroacoustics. Part 5 *Terms particular to electromedical equipment* Group 01 *Radiology and*

BIR Calendar Events

Unless otherwise indicated, enquiries about the following events should be addressed to the Assistant Secretary Programme, British Institute of Radiology, 36 Portland Place, London W1N 3DG (Tel. 01-580 4085).
The meetings are at 36 Portland Place unless otherwise stated.
Attendance is open to non-members

Annual General Meeting
The AGM of the British Institute of Radiology will be held at 4.30 pm on Wednesday, May 14, 1986 at 36 Portland Place, London W1.

Safety of Diagnostic Ultrasound and Presidential Address
May 15, 1986 at 2 pm
Middlesex Hospital Medical School, London W1
Speakers include Dr G. R. ter Haar, Dr F A. Duck, Dr A R. Williams and Dr P A. McKinney.

The Presidential Address will follow at 5.30 (open to non-registrants) to be given by Dr P. N T. Wells: "The prudent use of diagnostic ultrasound"
Joint BIR/BMUS/RSM/COR/IPSM/RCOG/RCR meeting.

Progress in Tumour Radiobiology
May 16, 1986 at 11.00 am
Organised by the Radiobiology Committee (proffered papers).

The Assurance of Quality in Medical Imaging
May 21, 1986
Middlesex Hospital Medical School, London W1
All-day meeting organised by the BIR Quality Assurance Working Party in conjunction with Industry Committee
Provisional speakers are Mrs M. J. Harvey, Mr S. Stuart, Mr I. R. F. Hendra, Dr C. Shaw, Dr J H. E Carmichael, Mr J. A. Garrett, Mrs O. Deaville, Dr P. Goddard, Dr G de Lacey, Mr M Fitzgerald and Miss F A. Paris.

Conversazione
June 19, 1986 at 7.00 pm
Royal Society of Medicine, London W1
Incorporating the Silvanus Thompson Memorial Lecture "Seeing through illusion", by Professor R L Gregory.

Joint RCR/BIR/RSM Autumn Provincial Meeting; RCR Annual General Meeting
September 11–13, 1986
University of Sheffield
Organised by the RCR. Further details from the Meetings Secretary, The Royal College of Radiologists, 38 Portland Place, London W1N 3PG (Tel. 01-636 4432/3).

Advance Notice

British Institute of Radiology 45th Annual Congress
incorporating the joint BIR/RCR/RSM (Section of Radiology) spring meeting

RADIOLOGY '87

Southampton April 1–3, 1987

The Congress will cover all aspects of radiology—X-ray diagnosis, radiotherapy, radiation oncology, nuclear medicine, ultrasound, NMR, radiological physics, radiobiology, radiation protection and related disciplines and is expected to include:

The Mayneord Lecture (BIR)
The George Simon Lecture (RCR)
The BIR Presidential Address
Major technical exhibition
Scientific exhibition

Proffered papers are invited Please apply for application form from the BIR. Absolute closing date for receipt of completed proffered paper forms is November 30, 1986

For further information please apply to the Assistant Secretary, Programme, The British Institute of Radiology, 36 Portland Place, London W1N 3DG (Tel. 01-580-4085)

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radiological physics terminology, published at the same time, contains terms and definitions to radiology and radiological physics. It supersedes BS 2579· 1955, which is now withdrawn.

Both groups relate to international standards Part 3 Group 08 is technically identical to Chapter 801 1984 of the International Electrotechnical Vocabulary (IEC) and Part 5 Group 01 to IEC Publication 50 (881): 1984 being an advance edition of Chapter 881 of the Vocabulary

Copies of BS 4727. Part 3: Group 08 and BS 4727 Part 5· Group 01 may be obtained from the Sales Department, British Standards Institution, Linford Wood, Milton Keynes MK14 6LE. Price· Part 3. Group 08 £31.00 (£12.40 to BSI subscribing members), Part 5 Group 01 £35 50 (£14.20 to BSI subscribing members)

3M Laser Imager now available
3M's Imaging Systems Division, St Paul, Minnesota, announces the immediate worldwide availability of its new laser imager system. The 3M Laser Imager is highly automated and capable of producing radiographic quality images from digital data sources such as CT, MRI, DSA and future digital radiography devices

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The new 3M Laser Imager will be sold to original equipment manufacturers and systems integrators as well as directly to medical institutions It replaces some of the conventional multiformat, multi-imaging video cameras. The Laser Imager was first shown to the UK medical market at the very successful BIR Radiology '85 Congress at UMIST.

For more information on the new 3M Laser Imager contact Gary Smith, 3M (UK) PLC, 3M House, PO Box 1, Bracknell, Berkshire RG12 1JU (Tel. 0344-58481).

Meetings, Courses, Notices

As a service to our readers, the title, date and place of meetings and contact address will be inserted free of charge: any additional information will be charged at £1.75 per printed line, per insertion. Please contact the Managing Editor.

European Gamma-11 Users Meeting

June 4–6, 1986
Guy's Hospital, London
Further details: E. D. Williams, Medical Physics Department, Sunderland District General Hospital, Sunderland SR4 7TP.

Cardiovascular Radiology and Musculoskeletal Radiology

June 12–15, 1986
Salzburg, Austria
Further details: Dr K. H. Barth, Department of Radiology, Georgetown University Hospital, Washington, DC 20007, USA (Tel. 202-625 2891).

Cambridge Meeting on Chest Disease

July 3–5, 1986
King's College, Cambridge
Further details: Dr C. D. R. Flower, Department of Radiology, Addenbrooke's Hospital, Hills Road, Cambridge.

The Leeds Gastroenterology Course for Radiologists

July 7–11, 1986
St James's University Hospital, Leeds
Further details: Mr Frank Moran, Senior Administrative Assistant, Postgraduate Dean's Office, Leeds General Infirmary, Leeds LS1 3EX (Tel. 0532-432 799, ext. 3631).

Nato Advanced Study Institute on: Physics and Technology of Hyperthermia

July 26–August 9, 1986
Urbino, Italy
Further details: Dr S. B. Field, MRC Cyclotron Unit, Hammersmith Hospital, Ducane Road, London W12 0HS.

International Symposium on Radiotherapy in Developing Countries

September 1–5, 1986
Vienna, Austria
Further details: Y. Skoropad, IAEA, Division of Life Sciences, PO Box 100, A-1400 Vienna, Austria.

Physics and Biology of Radiology

September 1–5, 1986
San Diego, California
Further details: R. Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113, USA (Tel. 404-641 9773).

Blood Vessel Imaging Using Ultrasound Techniques

September 4–5, 1986
Southampton General Hospital
Further details: Mr K. N. Humphries, Scientific Director, Vascular Unit, Medical Physics Department, Level D, Centre Block, Southampton General Hospital, Southampton SO9 4XY.

Organ Imaging Review: Toronto 1986

September 7–12, 1986
Four Seasons Hotel, Toronto, Canada
Further details: Dr E. Kassel, Program Co-ordinator, Department of Radiology, University of Toronto, Room 127 Fitzgerald Building, Faculty of Medicine, Toronto, Ontario, Canada M5S 1A8.

Paediatric Radiology Course

September 8–10, 1986
Sheffield
Basic paediatric imaging for consultants and senior registrars to enable them to face problems in the DGH and FRCR.
Further details: Dr G. M. Steiner, X-ray Department, Sheffield Childrens Hospital, Western Bank, Sheffield S10 2TH (Tel. 0742-71111).

2nd Annual Clinical Hyperthermia Symposium and Workshop

September 18–20, 1986
Mallinckrodt Institute of Radiology, St Louis, Missouri, USA
Further details: Dr B. Emami, Symposium Chairman, Division of Radiation Oncology, Mallinckrodt Institute of Radiology, Clinical Sciences Research Building–Suite 5500, 4939 Audubon Avenue, St Louis, Missouri 63110, USA.

Public Perception of Radiation

October 14, 1986
City Conference Centre, London
Further details: Programme Committee Secretary, Professor J. H. Martin, Department of Medical Biophysics, Building 15, Park Wynd, University of Dundee, Dundee DD1 4HN.

International Symposium: Malignant Disease in the Neck

November 12–14, 1986
Free University Hospital, Amsterdam, the Netherlands
Course Directors: G. B. Snow and R. M. Tiwari. Guest Faculty includes: R. L. Carter (UK), F. Demard (France), H. Goepfert (USA), J. Lang (W. Germany), R. Molinari (Italy), J. Overgaard (Denmark), E. M. Skolnik (USA), P. M. Stell (UK).

Further details: Department of Otolaryngology, Free University Hospital, de Boelelaan 1117, 1081 HV Amsterdam, the Netherlands.

Age-Related Factors in Radionuclide Metabolism and Dosimetry

November 26–28, 1986
Angers
Further details: Dr G. B. Gerber, Commission of the European Communities, DG XII/FI, Rue de la Loi 200, B-1049 Brussels, Belgium (Tel. 02-235 4041).

Conference on Health Effects of Low Dose Ionising Radiation: Recent Advances and Their Implications

March 31–April 3, 1987
Royal Institute of British Architects, London
Further details: The Secretariat, British Nuclear Energy Society at the Institution of Civil Engineers, 1–7 Great George Street, London SW1P 3AA (Tel. 01-630 0726).

Blood Flow '87 (Techniques in blood flow measurement and their relevance to clinical diagnosis)

July 7–8, 1987
University of Leeds
Further details: Mr R. Price, Department of Medical Physics, Leeds General Infirmary, Leeds LS1 3EX.

XI World Congress on Sarcoidosis and Other Granulomatous Disorders

September 6–11, 1987
Milan, Italy
Further details: PO XI WCS, Congress Studio, Via Cappuccio, 19, 20123 Milano, Italy.

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Written applications containing personal particulars, details of qualifications and experience, special interests, a record of present and previous appointments, list of publications and the names and addresses of three referees should be addressed to the **Medical Superintendent, Sir Charles Gairdner Hospital, Verdun Street, Nedlands, Western Australia 6009.**

Further information may be obtained from **Dr R. Thompson, A/Head, of Department of Radiology, (Telephone (09) 389 3333).**

Applications close Friday, 30 May, 1986.

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British Journal of Radiology
Supplement 17

Intended as a standard reference work on the subject, this replaces BJR Supplement 11, published in 1972, and contains typical values for all the types of radiation in common use today. Each chapter has been revised and updated wherever new data have become available: the principal extensions cover larger field sizes and longer SSDs for cobalt 60 gamma rays and megavoltage X rays, together with a wider coverage of megavoltage X rays, electrons and fast neutrons.
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For further information call or write to:
Dr W. M. Hryniuk, Director,
Ontario Cancer Foundation,
Hamilton Regional Centre,
711 Concession Street,
Hamilton, Ontario L8V 1C3
Canada
Telephone: (416) 387-9495

Canadian Immigration requirements state that preference will be given to Canadian citizens or landed immigrants.

Criteria and Methods for Quality Assurance in Medical X-ray Diagnosis

Proceedings of a Scientific Seminar organised by the Commission of the European Communities and the Centro di Ricerca Applicata e Documentazione, held in Udine, Italy, 17–19 April 1984

British Journal of Radiology Supplement 18

The contributors to this Seminar came from 15 European countries, the USA and Canada. All aspects of Quality Assurance were discussed: the concepts and implementation of QA, the involvement of research, professionals, industry and governments, and the technical aspects of equipment testing, image quality, information content and dose- and cost-reduction.

The proceedings give an up-to-date picture of the state of the art in QA and will be of interest to radiologists, radiographers, health physicists, radiation protection scientists, equipment manufacturers and administrators of health care programmes and radiation protection.

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Mailing address:

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Rhode Island Hospital
593 Eddy Street
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(continued from outside back cover)

Page

Early experience with combined interstitial hyperthermia and brachytherapy 525
P. R. C. Dunlop, R. J. Dickinson, J. W. Hand, A. J. Munro and K. A. Vallis

Correspondence

Dosimetry of the neutron beams at Hammersmith and Edinburgh 529
D. K. Bewley, C. J. Parnell and J. R. Williams

Diagnostic radiological examinations of women of reproductive capacity 529
J. G. B. Russell

Bleomycin lung: computed tomographic observations 530
S. K. Morcos

Reply
M. J. Rimmer, A. K. Dixon, C. D. R. Flower and K. Sikora

Phrygian cap updated? 530
S. Hamilton

Correction 440

Book reviews

Page

Linear accelerators for radiation therapy. Medical physics handbooks 17. *D. Greene* 452
Primary management of breast cancer. Alternatives to mastectomy. *J. S. Tobias and M. J. Peckham* (Eds) 452
Some issues important in developing basic radiation protection recommendations. NCRP proceedings No. 6. *T. M. Koval* (Ed.) 460
Radiation protection in the radiologic and health sciences, 2nd edit. *M. E. Noz and G. Q. Maguire Jr* 460
Future use of new imaging technologies in developing countries. Technical report series No. 723. *WHO Scientific Group* 460
Current topics in bioenergetics, Vol. 14. *C. P. Lee* (Ed.) 474
Radiology today 3. *M. W. Donner and F. H. W. Heuck* (Eds) 474
Computed tomography of CNS disease: a teaching file. *D. H. Yock Jr* 486
An introduction to emission computed tomography. IPSM report No. 44. *E. D. Williams* (Ed.) 486
Radiolabelled cellular blood elements. Pathophysiology, techniques and scintigraphic applications. *M. L. Thakur* (Ed.) 492
Diagnostic interventions in nuclear medicine. *J. H. Thrall and D. P. Swanson* (Eds) 492
Interventional real-time ultrasound. *H. Watanabe and M. Makuuchi* (Eds) 498
The pediatric spine. *D. S. Bradford and R. M. Hensinger* (Eds) 498
Iatrogenic disorders of the fetus, infant and child, Vol. II. *E. G. Kassner* (Ed.) 498
Radiopharmaceuticals and labelled compounds 1984. *IAEA* 504
Obstructive uropathy. *P. H. O'Reilly* (Ed.) 520
Paediatric neurosonography: clinical, tomographic and neuropathological correlates. *A. Q. Fischer, J. C. Anderson, R. M. Shuman and W. Stinson* 528

BIR Bulletin and Calendar Events *facing page* 530

VOL 59 NO 701 MAY 1986

The British Journal of Radiology

Contents

Page

A comparative review of the Hammersmith (1971–75) and Edinburgh (1977–82) neutron therapy trials of certain cancers of the oral cavity, oropharynx, larynx and hypopharynx 429
Medical Research Council Neutron Therapy Working Group

A Phase I study of mixed (neutron and photon) irradiation using two fractions per day in the treatment of high-grade astrocytomas 441
W. Duncan, J. McLelland, P. Davey, W. J. L. Jack, S. J. Arnott, A. Gordon, G. R. Kerr and J. R. Williams

Regional lung function impairment following post-operative radiotherapy for breast cancer using direct or tangential field techniques 445
S. Groth, A. Zaric, P. B. Sørensen, J. Larsen, P. G. Sørensen and N. Rossing

A comparison of the costs of vascular surgery and balloon dilatation in lower limb ischaemic disease 453
W. D. Jeans, R. M. Danton, R. N. Baird and M. Horrocks

The effects of introducing balloon dilatation into vascular surgical practice 457
W. D. Jeans, R. M. Danton, R. N. Baird and M. Horrocks

In vivo evaluation of myocardial infarction by computed tomography: an experiment with electrocardiographic gating 461
D. R. Checkley, T. Sekiya, I. Isherwood and J. Yates

A rational approach to the investigation of the gallbladder 471
P. G. Watson and S. R. Wild

Who has most epidural fat? Information from computed tomography 475
A. K. Dixon

Cholesterol granuloma of the facial skeleton 481
G. A. S. Lloyd

A prospective study of mammographic parenchymal patterns and risk of breast cancer 487
I. H. Gravelle, J. C. Bulstrode, R. D. Bulbrook, D. Y. Wang, D. Allen and J. L. Hayward

The measurement of limb blood flow using technetium-labelled red blood cells 493
A. Parkin, P. J. Robinson, P. A. Wiggins, S. H. Leveson, M. C. P. Salter, I. F. Matthews and F. M. Ware

Lack of discernible effect of diagnostic ultrasound on the chromosomes of cord blood lymphocytes exposed *in utero* 499
L. M. Henderson, S. Z. Aghamohammadi, C. F. Arlett and R. J. Cole

Case reports

Gastric emphysema demonstrated by computed tomography 505
D. F. Martin and G. Hartley

Ultrasonically guided fine-needle biopsy for histological sampling of suspect parathyroid tissue 507
S. Karstrup, A. Glenthøj, S. Torp-Pedersen, L. Nielsen and L. Hegedüs

Arteriohepatic dysplasia 509
T. Singcharoen, J. Partridge, W. D. Jeans and H. Baddeley

Solution to a knotty biliary drainage problem 511
S. K. Teplick and P. H. Haskin

Skeletal-muscle haemangioma presenting as an abdominal mass 513
M. Malone, R. de Bruyn and L. Spitz

Calcified post-traumatic renal pseudotumour 515
C. F. Loughran and F. M. Ehmke

Detection of *Toxocara* by computed tomography 518
B. Dupas, J. Barrier and P. Barre

Case of the month

An inevitable progression? 521
D. M. Hansell

Short communications

Radiotherapy employing three fractions in each day over a continuous period of 12 days 523
M. I. Saunders and S. Dische

(continued on inside back cover)

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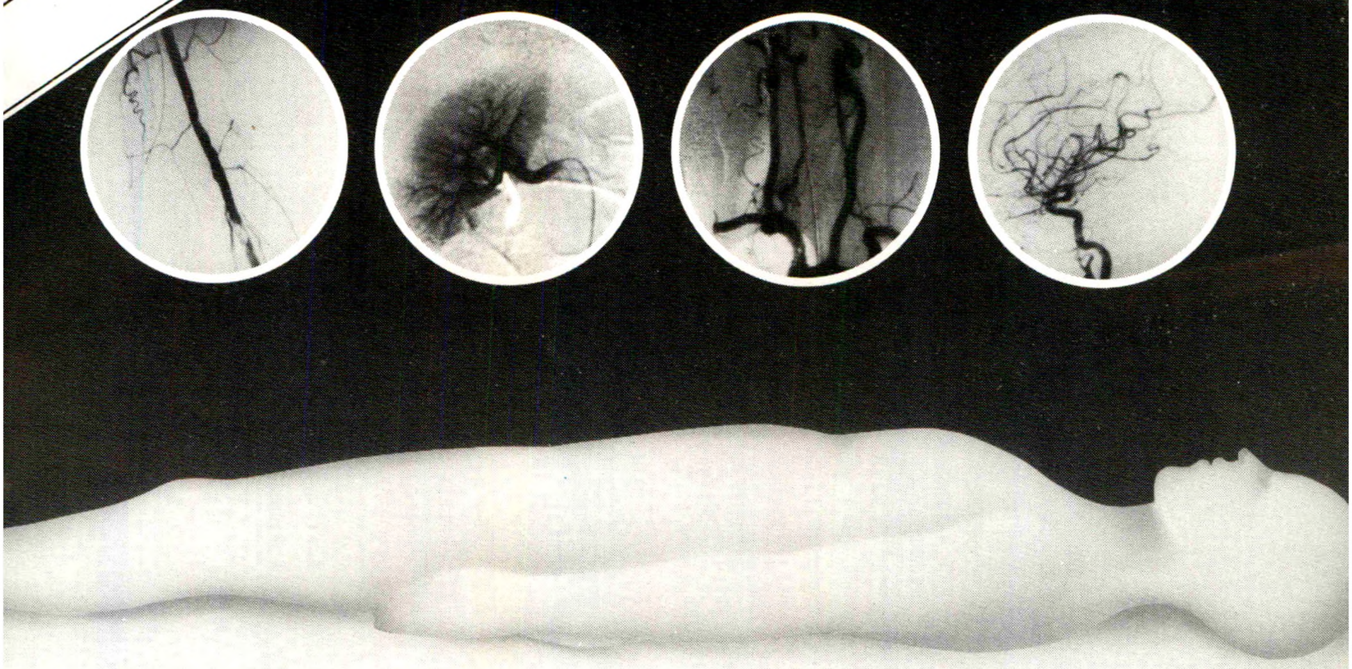

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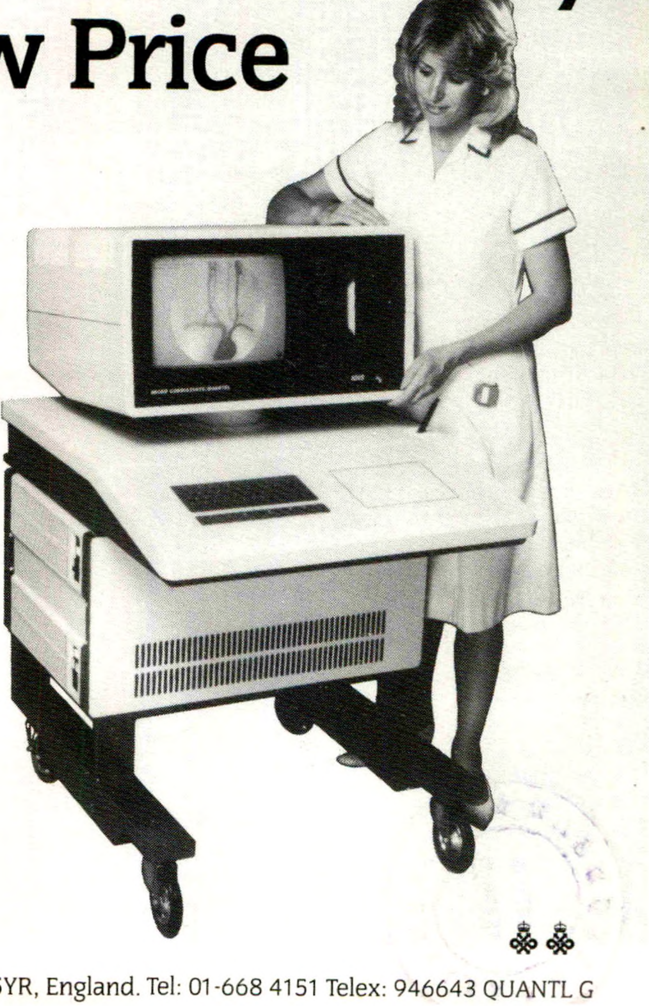

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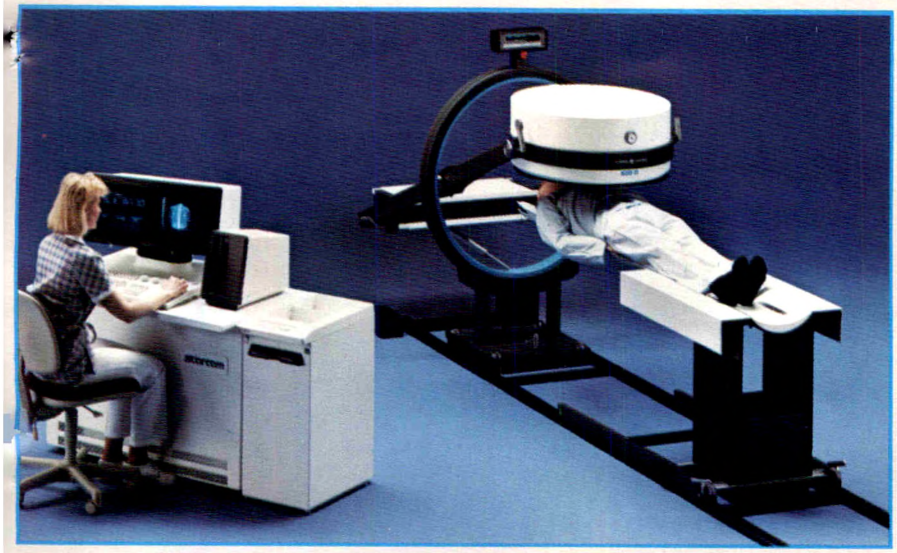

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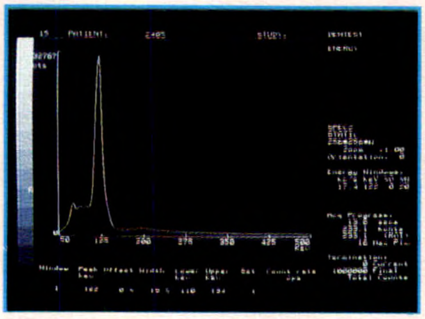

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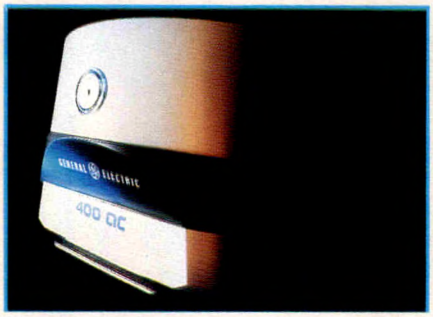

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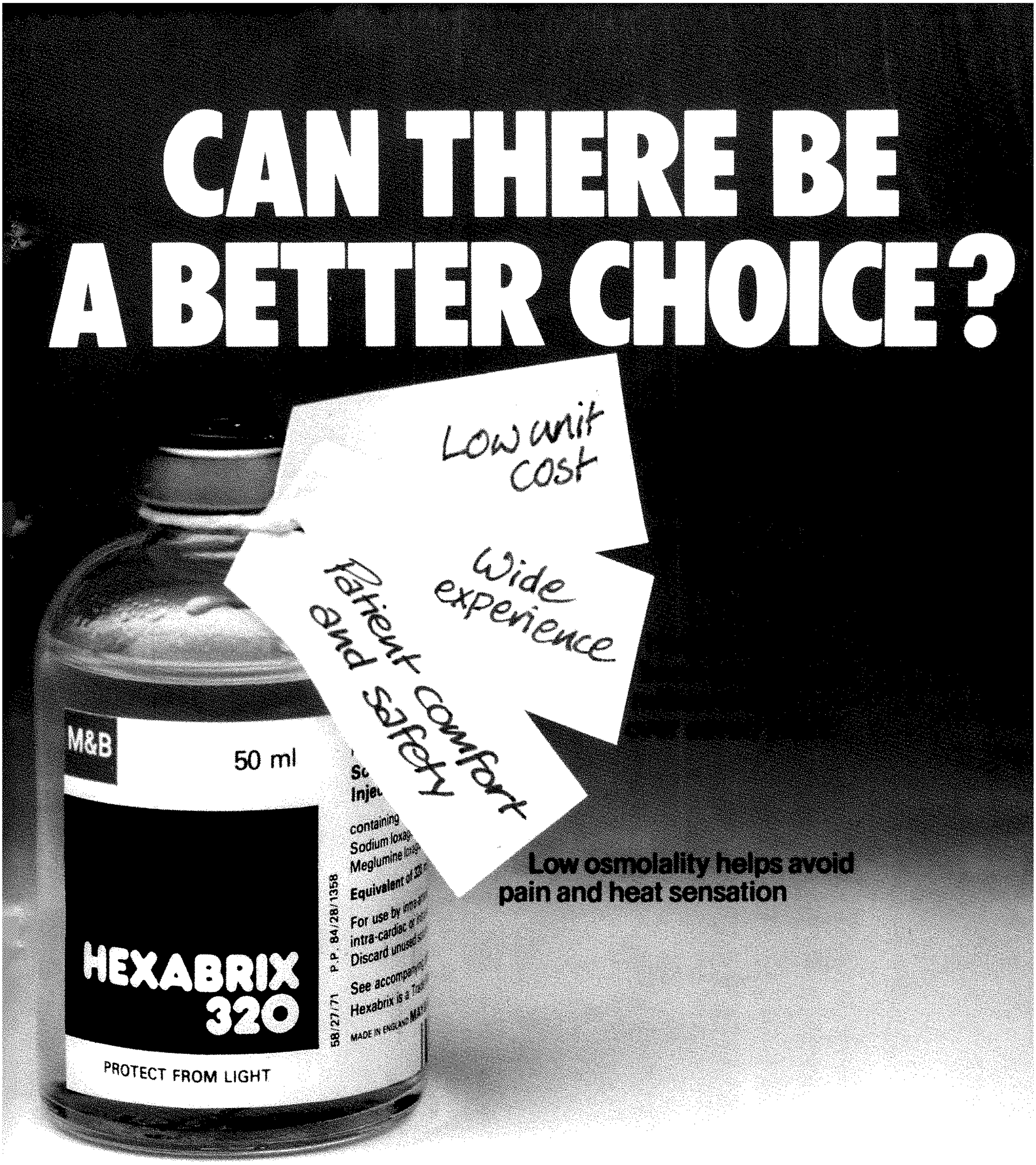

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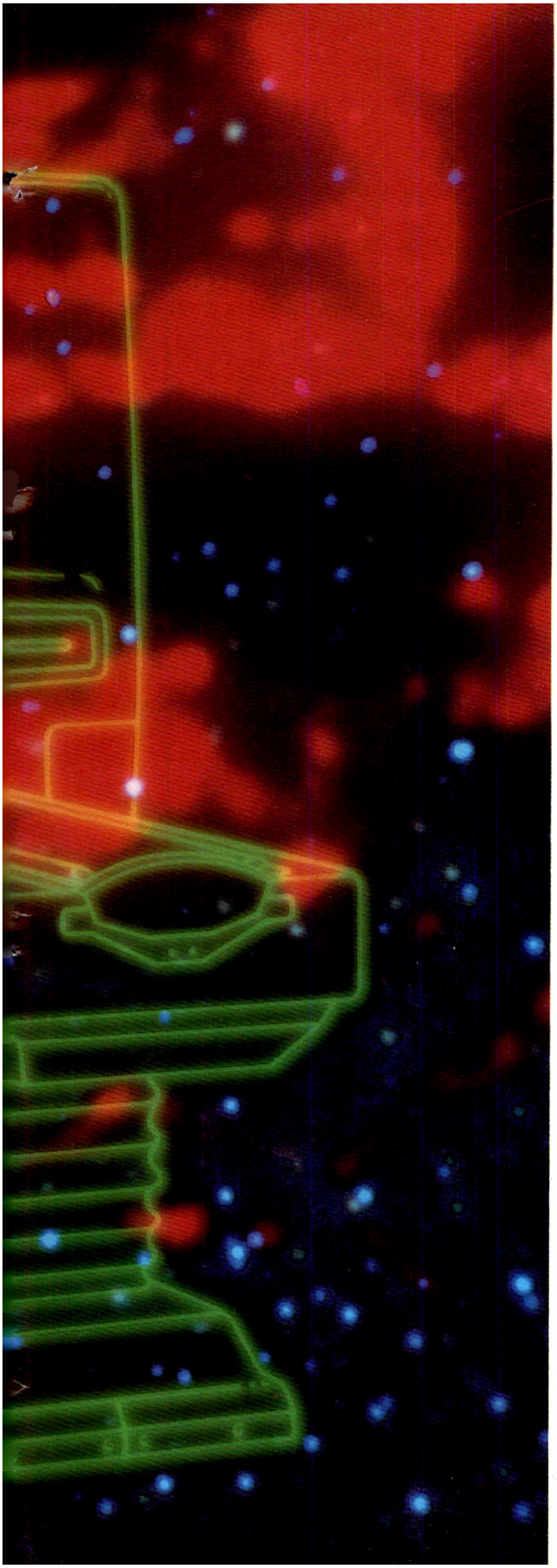

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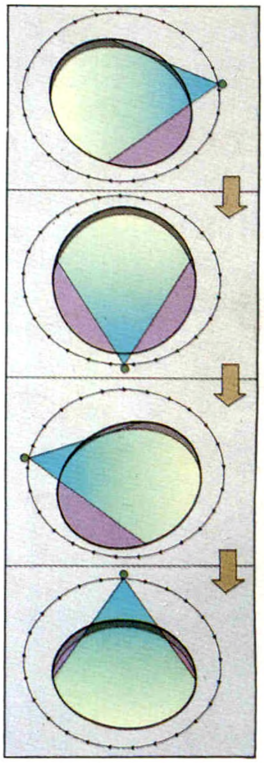

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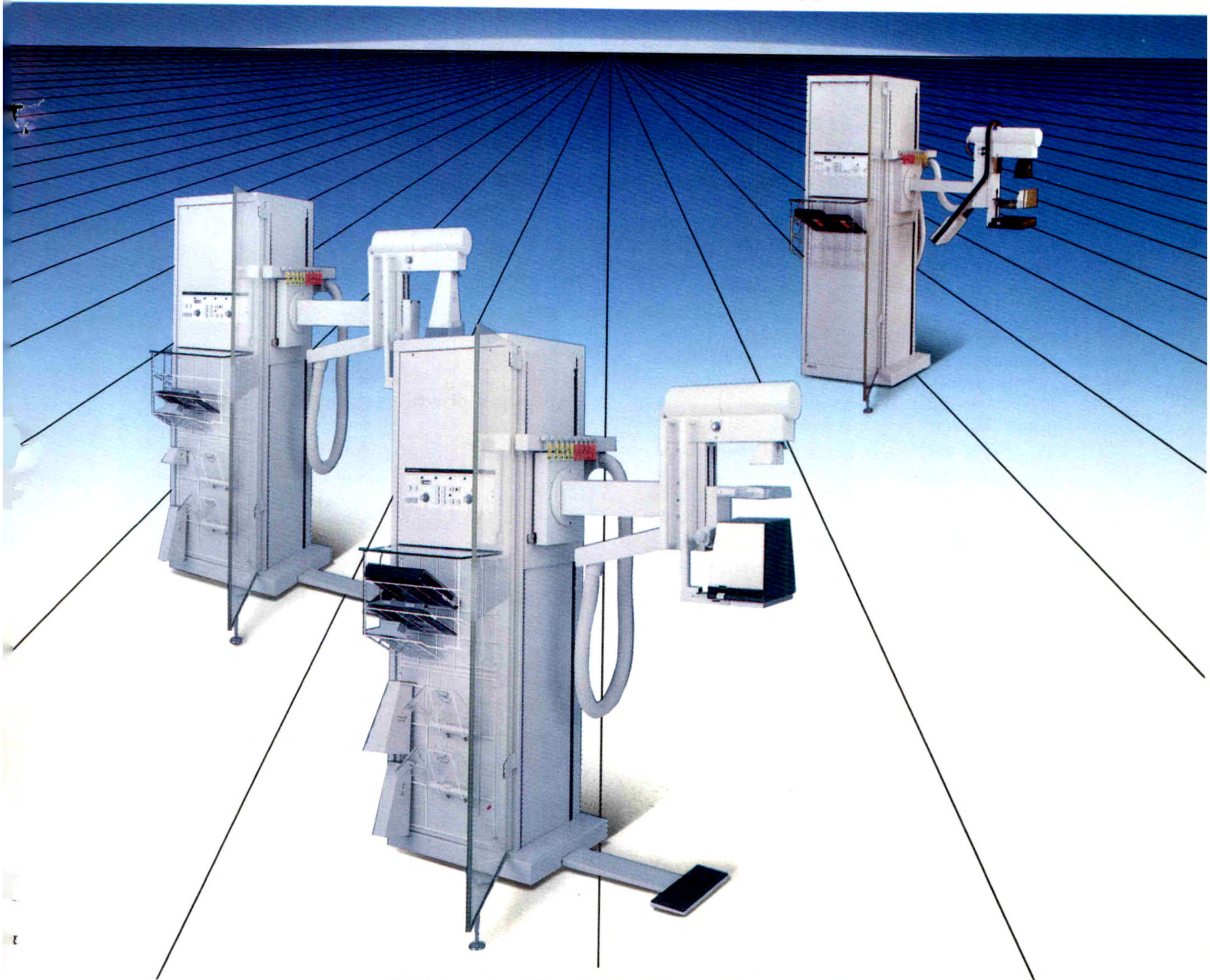

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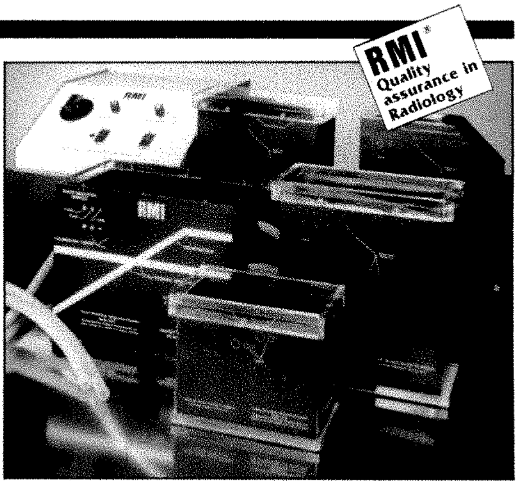

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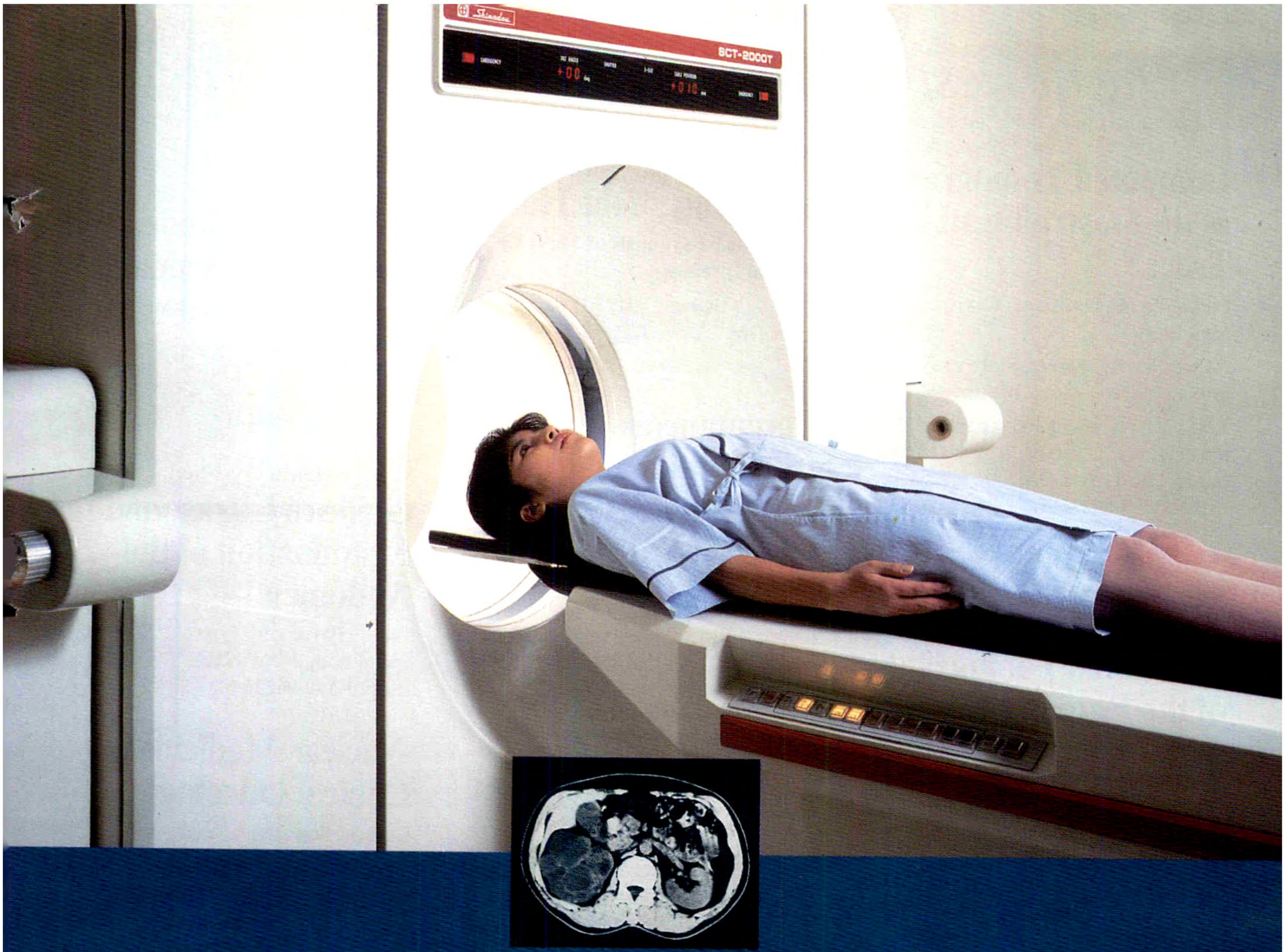

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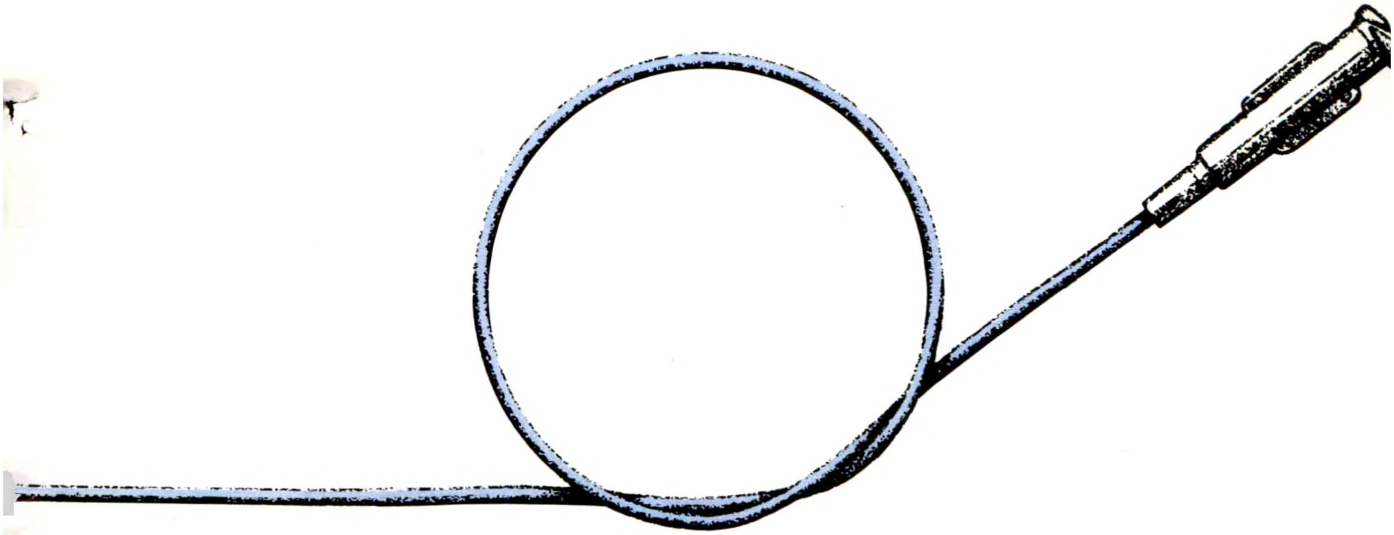

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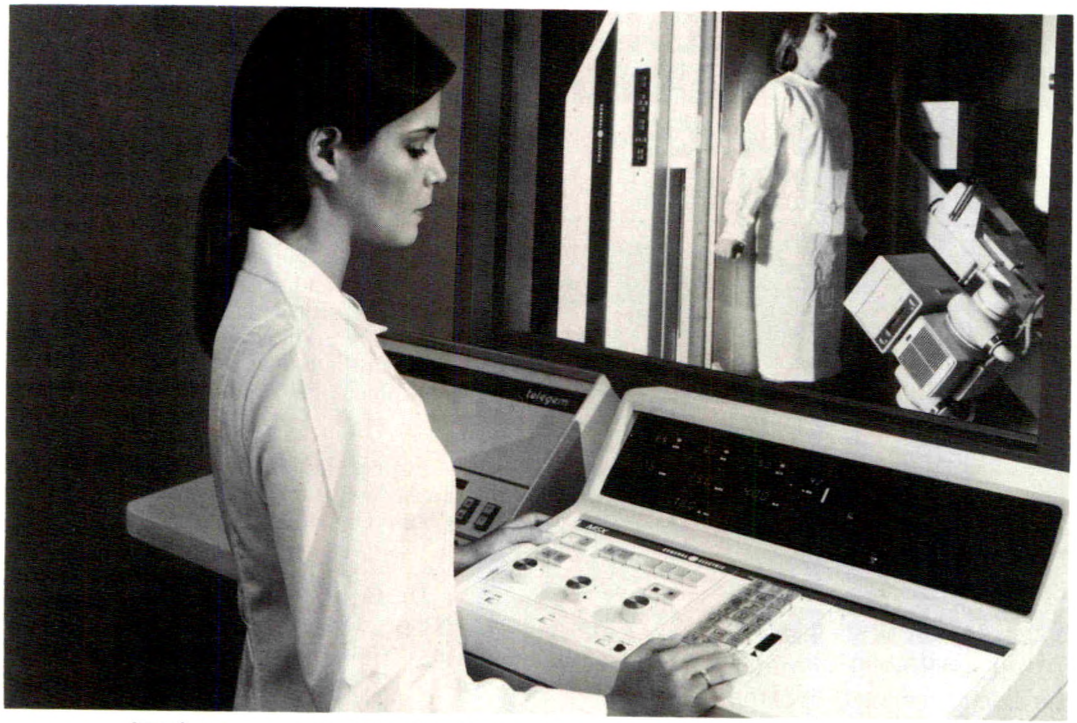

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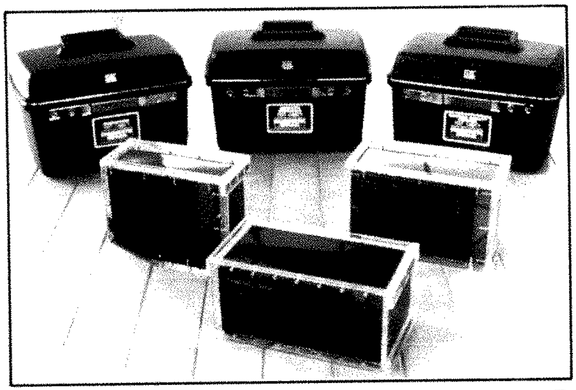

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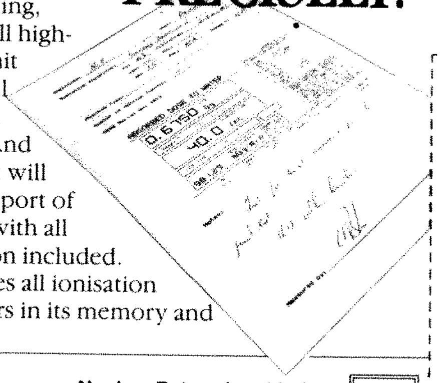

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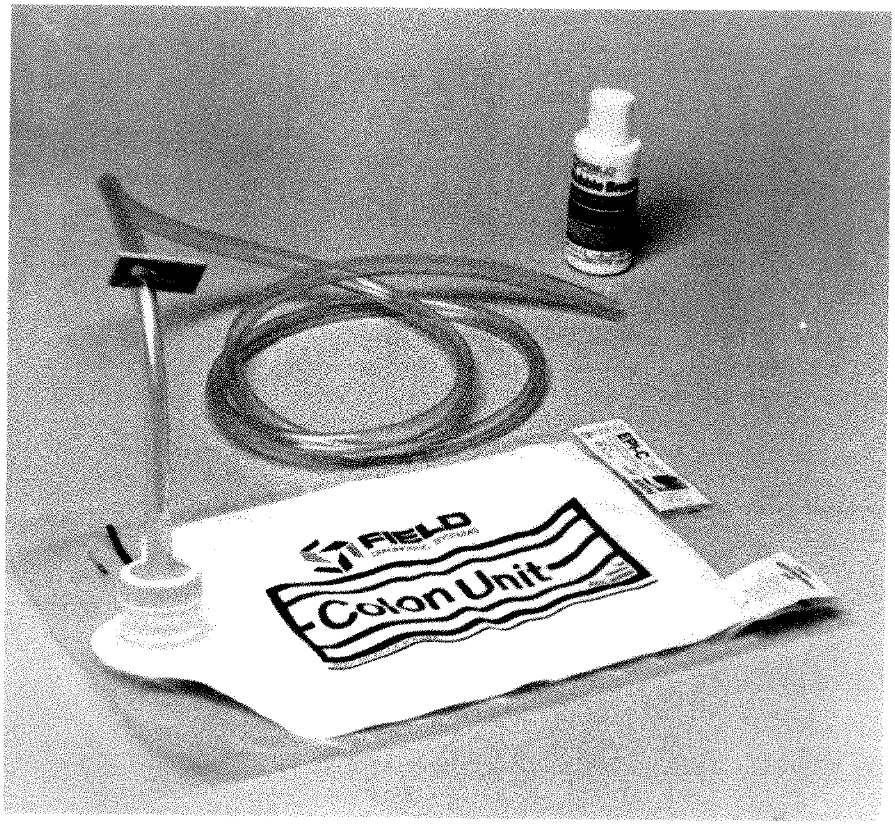

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The British Journal of Radiology

Reactions to radiographic contrast media: an attempt to detect specific anti-contrast medium antibodies in the sera of reactor patients

By *A. C. Walker, B.Sc. and †D. H. Carr, M.D.

University Department of Bacteriology & Immunology and †X-ray Department, Western Infirmary, Glasgow

(Received August 1985 and in revised form December 1985)

ABSTRACT

A radioimmunoassay was used in an attempt to detect specific anti-contrast medium antibodies in the sera of a group of 68 patients who reacted to radiographic contrast media and a group of 30 age-, sex- and disease-matched control patients who did not react. No evidence of specific antibodies of the IgG or IgE classes was demonstrated in these two groups. The results suggest the lack of an antibody-mediated aetiology for reactions to radiographic contrast media.

The mechanisms by which radiographic contrast media produce reactions in certain individuals remain poorly understood. It has been shown that contrast media affect a number of biological pathways. They have been shown to cause activation of the complement system (Arroyave et al, 1976; Lang et al, 1976; Kolb et al, 1978), induce histamine release directly from mast cells and basophils (Rockoff et al, 1970; Ring & Arroyave, 1979) and interact with the coagulation, fibrinolytic and kinin systems (Zir et al, 1974; Lasser et al, 1979; Neoh et al, 1981). Clinical observations, however, support an antibody-mediated mechanism for many reactions to contrast media (Brasch, 1980). General acceptance of this theory was hindered by the inability of workers to confirm the immunogenicity of the contrast-medium molecule (Lasser, 1968). Brasch et al (1976) reported the induction of specific antibodies to contrast-medium analogues in experimental animals and demonstrated elevated binding of radiolabelled contrast medium by the globulin fraction of sera from reactors, compared with controls. However, the validity of an antibody-mediated mechanism remains in dispute. Because of this situation, we have attempted to detect specific anti-contrast medium antibodies of the IgE and IgG classes in the sera of patients undergoing intravascular infusion of contrast medium. A radioimmunoassay technique was used to test the sera of both patients who manifested a reaction and patients who did not react.

MATERIALS AND METHODS

Collection of serum samples

Over a 3-year period, blood samples were collected from patients undergoing radiological examination. Blood was collected from an antecubital vein using a tourniquet before and immediately following injection of contrast medium. A second blood sample was obtained 12 days later from patients who manifested some form of reaction.

Serum was prepared by allowing the blood to clot at room temperature. The clotted samples were incubated at 37°C for 30 min and centrifuged at 400*g* for 15 min. The serum supernatant was removed using a Pasteur pipette and centrifuged again to remove any erythrocytes which were present. Following centrifugation, the serum samples were immediately frozen and stored at −70°C in 1 ml aliquots.

Reactor and non-reactor groups

Individuals were termed *reactors* if they physically manifested moderate to severe reactions, *i.e.* reactions ranging from rhinitis, nausea and vomiting, dyspnoea, oedema of face and extremities and urticaria to change

TABLE I

SYMPTOMS EXHIBITED BY REACTORS (SOME PATIENTS EXHIBITED MORE THAN ONE TYPE OF SYMPTOM)

Symptom	No. of patients
Urticaria	50
Pruritis	45
Bronchospasm	12
Laryngeal spasm	2
Sneezing	7
Hypotension	6
Pulmonary oedema	3
Abdominal pain	1
Angioneurotic oedema	1

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in blood pressure, change in neurological status, laryngeal spasm, bronchospasm and death. Table I shows the number of patients manifesting the different reactions. During the 3-year study in the Western Infirmary, one death occurred following the injection of contrast medium (diatrizoate used during angiography).

Non-reactors was the term applied to individuals who experienced no untoward effects during or following injection of contrast medium. Individuals experiencing minor effects, such as metallic taste in the mouth or feeling of heat, were also termed non-reactors. The non-reactor patients were age-, sex- and disease-matched with the reactors as far as possible and received the same contrast media.

Radiographic contrast media used

These were Biligram (methylglucamine ioglycamate 35%, 176 mg I/ml; Schering AG), Urografin 325 (sodium diatrizoate 40%, methylglucamine diatrizoate 18%, 325 mg I/ml; Schering AG), referred to in the text as ioglycamate and diatrizoate, respectively, ^{125}I-labelled ioglycamate and ^{125}I-labelled diatrizoate (Schering AG).

Binding of ^{125}I-labelled contrast medium to Sepharose particles

To 100 mg CNBr activated Sepharose 4B (Pharmacia) was added 0.35 ml bicarbonate buffer (0.1 M $NaHCO_3$, 0.5 M NaCl, pH 8.4); 37 kBq (1 μCi) ^{125}I-labelled ioglycamate (11.6 MBq/mg) or 37 kBq ^{125}I-labelled diatrizoate (23.3 MBq/mg) was added to the Sepharose suspension and the mixture allowed to stir overnight at room temperature. The mixture was then made up to 5 ml with bicarbonate buffer and centrifuged at 400*g* for 10 min. The amount of radiolabelled contrast medium contained in the supernatant and in the Sepharose pellet was measured in a gamma counter. The supernatant was discarded and the pellet washed several times in bicarbonate buffer. After each wash, the radioactivity of the supernatant and the Sepharose pellet was measured.

Binding of contrast medium to Sepharose for use in radioimmunoassay

CNBr activated Sepharose 4B particles (1 g) were suspended in 3.5 ml bicarbonate buffer (0.1 M $NaHCO_3$, 0.5 M NaCl, pH 8.4). A commercial sample of ioglycamate or diatrizoate was brought to pH 8.4 with 0.1 M NaOH and 10 ml of the contrast medium sample was added to the swollen Sepharose gel. The reaction mixture was made up to 20 ml with bicarbonate buffer and left mixing slowly overnight at 4°C. The gel was then centrifuged at 400*g* for 5 min and washed twice in bicarbonate buffer. To block the remaining active sites on the Sepharose particles, the gel was washed and mixed in ethanolamine/bicarbonate buffer (0.1 M ethanolamine in 0.1 M bicarbonate buffer, pH 8.4) for 2 h at 4°C. To complete the blocking procedure the gel was washed and allowed to stir for 1 h at 4°C in acetate buffer (50 ml 0.01 M sodium acetate in 0.2 M acetic acid made up to 100 ml volume with bicarbonate buffer). Finally, the gel was washed and resuspended in 10 ml 0.05% TritonX in PBS.

Radioimmunoassay

Equal volumes (250 μl) of contrast medium-linked Sepharose suspension were added to a series of tubes and 100 μl serum (neat or in doubling dilutions in normal saline) were added to each tube. The contents of each tube were mixed and incubated at room temperature for 1 h. The tubes were centrifuged at 400*g* for 5 min and the Sepharose particles washed four times in 0.05% TritonX in PBS to remove unbound serum constituents. The final supernatant was removed by aspiration and 150 μl ^{125}I-labelled rabbit anti-human IgE (Pharmacia) or ^{125}I-labelled sheep anti-human IgG (Scottish Antibody Production Unit, Law Hospital, Carluke) was added to each tube. The tubes were incubated at room temperature for 30 min with

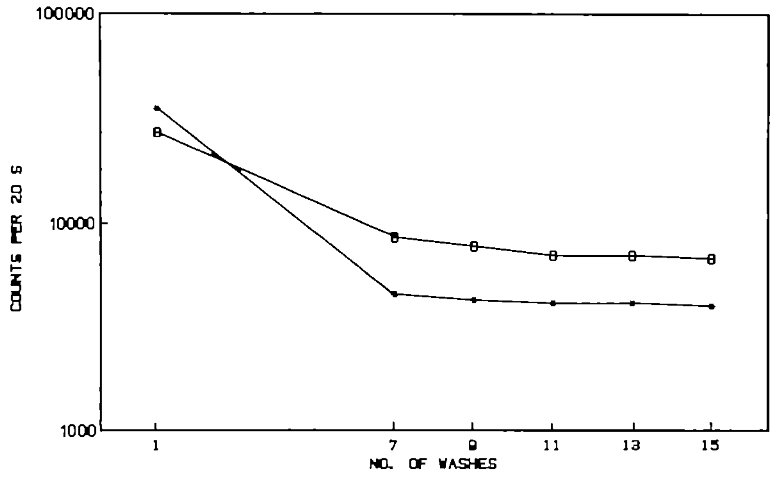

Fig. 1.

Binding of ^{125}I-labelled ioglycamate (□) and ^{125}I-labelled diatrizoate (×) to Sepharose.

TABLE II

BINDING OF REACTOR AND CONTROL SERUM IGG TO CONTRAST MEDIUM-LINKED SEPHAROSE

Group	Contrast medium used	No. of patients	Immediate post-injection sample (counts/min)	12-day post-injection sample (counts/min)
Reactor	Ioglycamate	10	18 400 ± 1430*	18 000 ± 1690
Non-reactor	Ioglycamate	10	19 000 ± 1350	
Normal sera	Ioglycamate	10	17 600 ± 1200	
Reactor	Diatrizoate	58	27 000 ± 1870	26 600 ± 3820
Non-reactor	Diatrizoate	20	25 200 ± 2700	
Normal sera	Diatrizoate	10	22 000 ± 2100	

*Standard error of mean.

frequent mixing. The tubes were centrifuged and the Sepharose pellet washed four times in 0.05% TritonX to remove free radiolabelled antibodies. The pellet was resuspended in 250 μl 0.05% TritonX and the radioactivity measured in a gamma counter. Assays using normal saline instead of serum were performed to determine the level of non-specific binding of the radiolabelled antisera. All tests were performed in duplicate.

Only samples from patients receiving ioglycamate or diatrizoate were tested in the radioimmunoassay. When comparing results obtained from reactor and non-reactor groups, both groups of patients had been administered the same contrast medium and tested for binding to the corresponding contrast medium-linked Sepharose preparation.

Statistical analysis

Student's *t*-test was used to assess the statistical significance of the data. A *p* value of < 0.05 was taken to indicate a significant difference.

RESULTS

Binding of radiolabelled contrast medium to Sepharose

Satisfactory binding of ^{125}I-labelled ioglycamate and ^{125}I-labelled diatrizoate to Sepharose was obtained (Fig. 1). Percentage labelling was calculated by the number of counts in the final pellet (after 15 washes) divided by the number of counts in the original mixture (pellet + supernatant) multiplied by 100. Binding for ioglycamate was 6% and for diatrizoate, 2%.

Binding of serum IgG and IgE to contrast medium-linked Sepharose

Table II shows the mean level of IgG bound in the sera of reactor and non-reactor patients. No significant difference was observed between reactors and controls. It was also observed that no significant differences in IgG binding was found when immediate post-injection serum samples were compared with 12-day post-injection samples in the reactor patient group. However, considerably higher levels of binding were found in the serum of two patients from this group: one reacted to ioglycamate, the other to diatrizoate. Standard curves were obtained when serial dilutions of these "standard" sera were tested (12-day post-injection sample).

In order to determine whether the IgG binding measured was due to specific antibody binding to the Sepharose-linked contrast medium or non-specific binding of IgG to the Sepharose particles, 100 μl

TABLE III

BINDING OF SERUM IGG TO CONTRAST MEDIUM-LINKED AND UNLINKED SEPHAROSE IN REACTORS AND CONTROLS

Group	Contrast medium administered	No. of patients	Sepharose used in radioimmunoassay	Immediate post-injection sample (counts/min)
Reactor	Ioglycamate	10	Ioglycamate-linked	18 000 ± 2300*
Reactor	Ioglycamate	10	Unlinked	19 700 ± 2500
Non-reactor	Ioglycamate	10	Ioglycamate-linked	19 700 ± 8400
Non-reactor	Ioglycamate	10	Unlinked	13 500 ± 2300
Reactor	Diatrizoate	58	Diatrizoate-linked	72 800 ± 2600
Reactor	Diatrizoate	58	Unlinked	85 100 ± 6400
Non-reactor	Diatrizoate	20	Diatrizoate-linked	63 700 ± 4900
Non-reactor	Diatrizoate	20	Unlinked	89 000 ± 4600

*Standard error of mean.

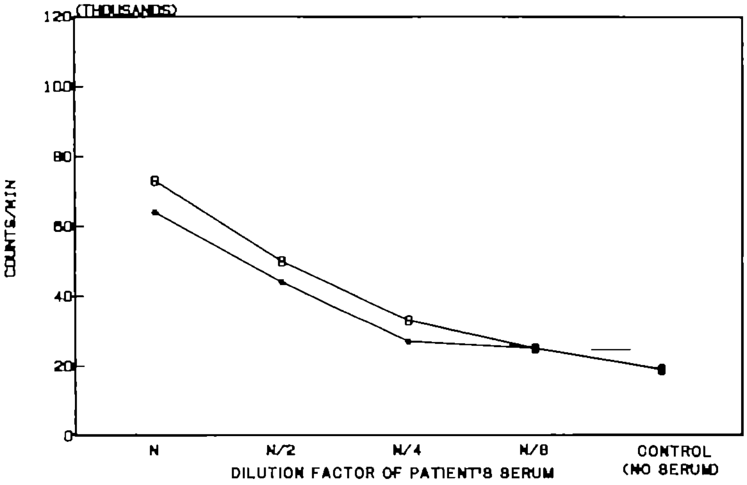

FIG. 2.

IgG binding of human antigluten antiserum to gluten-linked Sepharose. □ represents no soluble ioglycamate added to the serum; × represents soluble ioglycamate added to the serum N = neat serum.

soluble contrast medium (or 100 μl normal saline was added to 100 μl "standard" sera before being tested. Addition of soluble contrast medium caused an inhibition of IgG binding.

To demonstrate clearly the presence or absence of specific anti-contrast medium antibodies, serial dilutions of the "standard" sera were tested using contrast medium-linked Sepharose and unlinked Sepharose, that is, Sepharose prepared as before in the absence of contrast medium. The IgG binding of sera from the reactor patients and control sera were measured also using both Sepharose preparations. The results demonstrated that serial dilutions of the "standard" sera gave the same level of IgG binding with contrast medium-linked Sepharose and unlinked Sepharose The results in Table III show that there was no significant difference in IgG binding between reactor and non-reactor groups and this was unaffected by the absence or presence of contrast medium linked to the Sepharose particles. The results strongly suggest that non-specific binding of IgG to the Sepharose particles was measured in the assay.

Contrast medium can cause inhibition of the binding of antisera to other antigens, *i.e.*, the inhibition of binding of anti-gluten antiserum to Sepharose-linked gluten (Fig. 2).

Similar experiments were performed in an attempt to detect specific anti-contrast medium IgE antibodies in the serum of patients. Assays were performed as described above using ^{125}I-labelled rabbit anti-human IgE antiserum. Tables IV and V show the level of IgE binding to contrast medium-linked Sepharose and unlinked Sepharose found in the sera of reactors and controls. It was observed that almost no IgE was bound to either Sepharose preparation when reactor and control group sera were tested. There were no significant differences in the level of IgE binding between immediate post-injection samples and 12-day post-injection samples.

DISCUSSION

The results demonstrate no significant differences in the binding of serum IgG and IgE to Sepharose-linked contrast medium between the reactor group and the non-reactor group. Neither group of patients' sera showed increased binding compared with normal human control sera. The higher level of IgG binding found in the sera of two patients from the reactor group

TABLE IV

BINDING OF SERUM IGE TO CONTRAST MEDIUM-LINKED AND UNLINKED SEPHAROSE IN REACTORS AND CONTROLS (IOGLYCAMATE)

Group	Contrast medium administered	No. of patients	Sepharose used in radioimmunoassay	Immediate post-injection samples (counts/min)	12 day post-injection sample (counts/min)
Reactor	Ioglycamate	10	Ioglycamate-linked	343±15*	344±12
Non-reactor	Ioglycamate	10	Ioglycamate-linked	315±14	
Normal sera	—	10	Ioglycamate-linked	372±35	
Reactor	Ioglycamate	10	Unlinked	321±34	340±21
Non-reactor	Ioglycamate	10	Unlinked	301±26	
Normal sera	—	10	Unlinked	305±18	

*Standard error of mean

TABLE V

BINDING OF SERUM IGE TO CONTRAST MEDIUM-LINKED AND UNLINKED SEPHAROSE IN REACTORS AND CONTROLS (DIATRIZOATE)

Group	Contrast medium administered	No. of patients	Sepharose used in radioimmunoassay	Immediate post-injection samples (counts/min)	12-day post-injection sample (counts/min)
Reactor	Diatrizoate	58	Diatrizoate-linked	424±29*	410±32
Non-reactor	Diatrizoate	20	Diatrizoate-linked	453±42	
Normal sera	—	10	Diatrizoate-linked	444±20	
Reactor	Diatrizoate	58	Unlinked	452±34	423±18
Non-reactor	Diatrizoate	20	Unlinked	421±19	
Normal sera	—	10	Unlinked	435±25	

*Standard error of mean.

was subsequently shown to be non-specific. The inhibition of IgG binding by soluble contrast medium was also shown to be non-specific inhibition, the contrast medium ioglycamate being able to inhibit partially the binding of anti-gluten antiserum to gluten bound to Sepharose. This inhibition may be due to the high viscosity of commercial solutions of contrast medium. Therefore, using the radioimmunoassay described, specific antibodies to diatrizoate or ioglycamate of the IgE or IgG classes could not be demonstrated in the sera of reactor patients.

The fact that specific antibodies were not detected here, does not mean their presence can definitely be excluded. It is possible that the techniques used were not sensitive enough or that antibodies of another class (IgM or IgA) may be present.

In the above group of 68 patients who manifested a reaction when administered contrast medium, specific antibodies were not found. However, that is not to say individuals do not exist who possess specific antibodies to contrast-medium molecules and, consequently, suffer an immediate hypersensitivity reaction when administered contrast medium for diagnostic radiological purposes. There have been reports of specific antibodies found in the sera of patients suffering an adverse reaction. Kleinknecht et al (1974) demonstrated an IgM antibody directed against sodium iothalamate in a patient who developed renal failure after administration of the contrast medium. Wakkers-Garritsen et al (1976) reported a patient exhibiting an IgE antibody to a cholangiographic contrast medium. Intravenous injection of contrast medium in a patient with Waldenstrom's macroglobulinaemia resulted in intravascular precipitation and sudden death (Bauer et al, 1974). It was subsequently found that, *in vitro*, the patient's monoclonal IgM reacted with the dimeric contrast medium used (ioglycamate) to cause precipitation. Passive transfer experiments in mice with the patient's monoclonal IgM resulted in death after injection of the contrast medium (Harboe et al, 1976).

Although Brasch et al (1976) demonstrated elevation of the binding of radiolabelled contrast medium by the globulin fraction of sera from reactors compared with controls, a significant proportion of the reactors did not have raised binding levels and, conversely, some of the controls were shown to have binding levels as high as those of reactors. The failure of other workers to detect specific antibodies to contrast medium in the sera of patients who have suffered a reaction (Lasser, 1968) and, similarly, the failure to induce hypersensitivity reactions to radiographic contrast media in experimental animals (Dunn et al, 1975) support the data reported above. The data are consistent with the evidence from work performed in experimental animals where techniques specifically designed to produce favourable conditions for the production of anti-contrast medium IgE antibodies failed to induce antibody production (Carr & Walker, 1984). It seems likely, therefore, that the majority of adverse reactions to contrast media do not have an antibody-mediated aetiology.

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Tissue analysis by dual-energy computed tomography

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Abstract

A straightforward method of tissue analysis from dual-energy computed tomography (CT) is presented which does not rely on previous inaccurate or incorrect formulations of the X-ray attenuation coefficient. The attenuation coefficients of tissue and bone were represented by a mixture of two reference materials. For convenience, water and calcium chloride were chosen. After careful calibration of the CT scanner, a dual-energy CT scan yields the water and calcium chloride "coefficients", the concentration of water and calcium chloride in units of kg/kg multiplied by the specific gravity of the tissue. For an error of ±2 HU on dual-energy scans at 140 kVp and 87 kVp on an EMI CT5005 general-purpose scanner, the error on the calcium chloride coefficients is ±0.004 kg/kg. Fat concentrations greater than 25% by weight may be detected when the coefficients are averaged over at least 200 pixels. Bone mineral content could be measured with a precision of 0.01 (in units of kg/kg multiplied by specific gravity) for averaging regions of 24 pixels. Iodine concentrations in tissue can be deduced if water and iodine are chosen as the reference materials. Clinical examples are presented to illustrate the technique for scans of both the head and the abdomen.

Since the first dual-energy CT techniques were proposed by Rutherford et al in 1976 there has been considerable interest in its application to tissue characterisation (Dubal & Wigli, 1977; Isherwood et al, 1977; Marshall et al, 1977; Latchaw et al, 1978; Di Chiro et al, 1979), radiotherapy treatment planning (Henson & Fox, 1984) and bone densitometry (Genant & Boyd, 1977; Adams et al, 1982; Dunscombe et al, 1984). However, we have shown that these techniques rely on an incorrect formulation of the X-ray attenuation coefficient, either using the spectral factor approach or by defining an effective atomic number of the material (Hawkes & Jackson, 1980; Jackson & Hawkes, 1981).

We have shown experimentally (Jackson & Hawkes, 1983) that the spectral factor approach can lead to significant errors. Depending on the interpretation given to the results of the dual-energy analysis, these errors may lead directly to significant errors in, for example, the determination of mineral concentration in bone, or fat content in tissue.

We present here a simple method of calibration and computation in dual-energy CT which does not rely on previous, incorrect formalisms of the attenuation coefficient. We make use of the result that the attenuation of X-rays by tissue is equal to that of a hypothetical mixture of two suitable calibration materials. The composition of this hypothetical mixture does not change with X-ray energy and, hence, characterises the tissue. Dual-energy CT permits the derivation of this composition.

Lehmann et al (1981) have proposed a similar division of the attenuation coefficient into two basis sets. However, they assumed, incorrectly, that the attenuation coefficient may be expressed as a sum of photoelectric and Compton components whose energy dependence is tissue dependent.

Method

Theory

We have already shown that the attenuation coefficients of different tissues and bone may be represented by a mixture of only two reference materials (Kouris et al, 1982). Water and calcium chloride may be chosen as examples of the reference materials. The mass

TABLE I

THE COEFFICIENTS a_w AND a_c, FROM EQUATION (1)*

Tissue components and chemicals used to represent tissue	The coefficients a_w (kg/kg)	The coefficients a_c (kg/kg)
Muscle†	0.9886	0.0026
Muscle‡	0.9872	0.0029
Muscle§	0.9890	0.0030
Blood‡	0.9881	0.0031
Liver‡	0.9921	0.0017
Fat‡	1.0377	−0.0356
Protein‡	0.9835	−0.0228
Carbohydrate‡	0.9640	−0.0119
Hydroxyapatite	0.3217	0.6558
Compact bone†	0.7525	0.2310
Cortical bone‡	0.6380	0.3435
Femur§	0.5457	0.4564
Bone mineral	−0.0770	1.1037

*These define hypothetical mixtures of water and calcium chloride whose mass attenuation coefficients are equal to those tissues and tissue components shown for the energy range 30 keV to 200 keV.

Data on atomic composition were obtained from †ICRU (1964), ‡ICRP (1975) and §Kim (1974). Bone mineral was taken as 32.3% phosphorus and 67.7% calcium by weight.

attenuation coefficient, $U(E)$, of the tissue at energy E can be written as:

$$U(E) = a_w U_w(E) + a_c U_c(E) \quad (1)$$

where a_w and a_c have dimensions of kg/kg and may take negative values, and w and c refer to water and calcium chloride. The coefficients a_w and a_c were calculated by a best fit to the mass attenuation coefficients of tissue, water and calcium chloride. Coefficients for various tissues and tissue components are listed in Table I. The mass attenuation coefficients were calculated using the tabulations of Hubbell (1982) and the mixture rule. The attenuation coefficients calculated from Equation (1) were within 0.5% of those calculated directly using the mixture rule and the known elemental composition, over an energy range of 30–200 keV. This is well within the accuracy of tabulated attenuation coefficients.

Neglecting beam hardening and other calibration errors, the correct Hounsfield number may be written (Brooks, 1977) as:

$$H = 1000(\bar{\mu} - \bar{\mu}_w)/\bar{\mu}_w \quad (2)$$

where $\bar{\mu}$ and $\bar{\mu}_w$ are the spectrum-dependent linear attenuation coefficients for the tissue and water, respectively, obtained by integrating the monoenergetic attenuation coefficient over the normalised detected energy-spectrum. In practice, however, the CT scanner yields Hounsfield numbers H_M, which must be related to the true Hounsfield scale using the equation (Brooks, 1977):

$$H = 1000(H_M - H_w)/(H_w - H_a) \quad (3)$$

where H_w is the measured Hounsfield number for water and H_a is the measured Hounsfield number for air.

Equation (1) may be rewritten to yield the linear attenuation coefficient for tissue, $\mu(E)$, in the form:

$$\mu(E) = \rho_w(m_w U_w(E) + m_c U_c(E)) \quad (4)$$

where the dimensionless coefficients m_w and m_c are given by:

$$m_w = (\rho/\rho_w)a_w$$
$$m_c = (\rho/\rho_w)a_c$$

and (ρ/ρ_w) is the specific gravity of the tissue, ρ is the density of the tissue and ρ_w is the density of water. Hence, substituting in Equation (2) yields:

$$H = 1000\,(m_w - 1) + m_c\phi_c \quad (5)$$

where

$$\phi_c = 1000(\bar{U}_c/\bar{U}_w)$$

and $\bar{U}_c$ and $\bar{U}_w$ are the mass attenuation coefficients of calcium chloride and water integrated over the normalised detected energy spectrum.

Combining Equations (3) and (5) yields:

$$1000(H_M - H_w)/(H_w - H_a) = 1000(m_w - 1) + m_c\phi_c \quad (6)$$

In a practical dual-energy experiment the CT scanner is calibrated for each X-ray spectrum as follows. The Hounsfield number of water, H_w, is found by scanning water and the Hounsfield number of air, H_a, is found by scanning a small vial containing air. The factor ϕ_c is found by scanning a small vial containing an aqueous solution of calcium chloride of known concentration and substituting the values of H, m_w and m_c in Equation (5). For a tissue of unknown composition the Hounsfield number, H_M is measured for each X-ray spectrum and substitution in Equation (6) yields two simultaneous equations which may be solved for m_w and m_c. These values of m_w and m_c, the water and calcium chloride "coefficients", characterise the tissue.

The derivation does not rely on the use of a spectral factor or an effective energy of the X-ray spectrum. Neither does it rely on the existence of effective atomic number of photoelectric coefficients which, it has been shown, are neither rigorously defined (Jackson & Hawkes, 1981) nor accurately energy-independent coefficients of low-atomic-number mixtures such as tissue (Jackson & Hawkes, 1983).

When iodine is used to enhance certain regions of tissue and the iodine concentration in tissue is required, iodine should be used instead of calcium chloride as the second reference material. The small iodine coefficients of the unenhanced tissue can be found, either by extrapolation from adjacent regions in the scan or by dual-energy scanning before the injection of contrast material. The iodine concentration in tissue is given by the difference in iodine coefficients between the enhanced and the unenhanced scans.

Experiment

The calibration materials (air and calcium chloride or iodine solutions) were contained in polythene vials of 25 mm internal diameter. These were inserted in cylindrical perspex phantoms containing water. For abdominal studies the phantom diameter was 320 mm, while for studies of the head the phantom diameter was 240 mm. All scans were performed on the EMI CT5005 general-purpose CT scanner at the Royal Marsden Hospital. The two different spectra were achieved by setting the X-ray voltages to 140 kVp or 87 kVp (which were the highest and lowest voltages obtainable on the CT scanner). The filtration of the X-ray beam was the same for each spectrum.

The calcium chloride solution used was approximately 5% by weight calcium chloride and the iodine solution used was approximately 0.4% by weight iodine. These solutions were of sufficient concentration to yield reliable values for the factor ϕ_c on the EMI CT5005, yet not so concentrated as to result in significant beam-hardening errors. In initial experiments several solutions were made up to ensure that the values of ϕ_c were independent of the concentration, m_c, for the mixture used for routine calibration purposes.

The scanning procedure was as follows. At the desired slice, one scan was taken at 140 kVp. On completion of this scan the tube voltage was reduced to 87 kVp and another scan was taken. For the head scan the reconstructed field of view was 240 mm with a 70 s scan time, while for abdominal scans the field of view was 320 mm with a 20 s scan time. Plastic bolus material was packed around the patient to provide an approximately circular cross-section. Obvious markers, such as bone–tissue interfaces and the patient outline, were used as a check to ensure that there had been no patient movement between the two scans.

Using the EMI independent viewing console, the average Hounsfield number was calculated over the required region of interest for each image and the water and calcium chloride or iodine coefficients were derived using Equation (6).

Accuracy of technique

The evaluation of propagation of errors in Equation (6) is straightforward. In a study on the EMI CT5005 we found that, for integration over large areas of the same tissue in repeated scans of the same patient, the error in the mean Hounsfield number was about ± 2 (one standard deviation) (Hawkes et al, 1981), provided that there were no visible artefacts, such as streaks crossing the region of interest. This error was due to the beam-hardening effect, errors in the calibration of the scanner, patient movement, variation in X-ray tube current and voltage, drift in detector gain and the partial-volume effect. All these errors are machine- or patient-dependent, but are potentially correctable.

Beam-hardening errors are strongly dependent on the shape of the patient outline and errors increase with the presence of large regions of bone, iodine-enhanced tissue or air. If care is taken to pack plastic bolus around the patient, to present an approximately circular cross section to the scanner, and provided regions for analysis were further than 10 mm from large regions of bone, phantom work on the EMI CT5005 showed that beam-hardening errors were less than 2 HU. In the vicinity of large areas of bone the beam-hardening error increases considerably. For example, phantom work showed that the centre of $75\ \text{mm}^2$ of calcium chloride solution, which had a Hounsfield number of 458, and was approximately equivalent to cortical bone, the beam-hardening error was found to be 11 HU. The tube voltage was 140 kVP and the vial containing the calcium chloride solution was placed at the centre of a cylindrical water phantom of 320 mm diameter. The error due to beam hardening of the calcium chloride coefficient of this solution was 0.009 from dual-energy

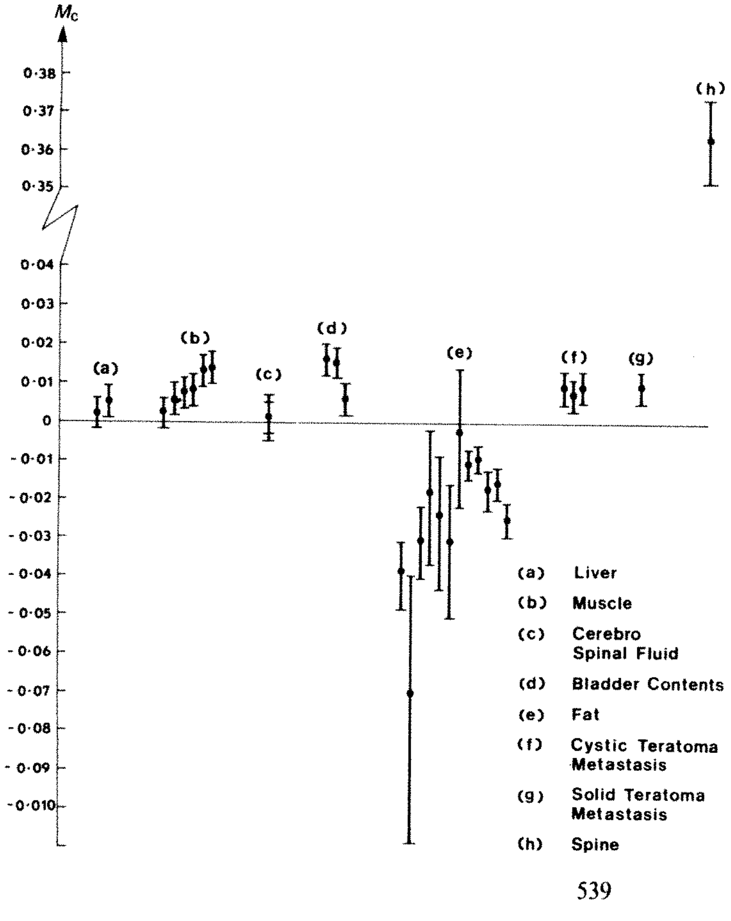

FIG. 1.

Values of the calcium chloride coefficient, m_c, obtained from different regions in abdominal scans of two patients.

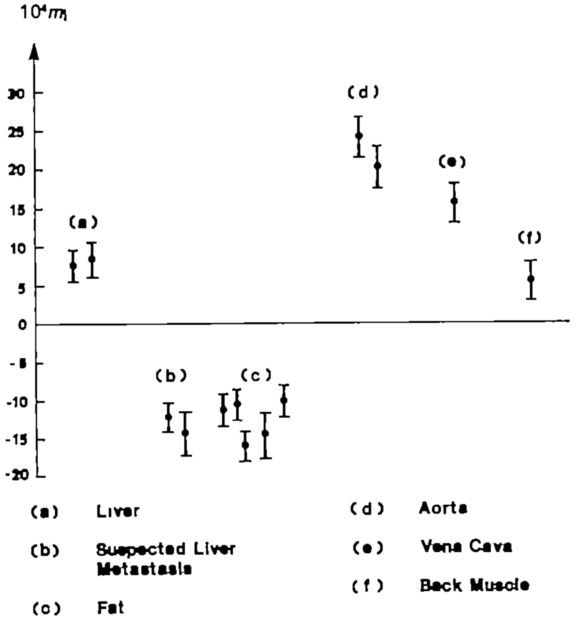

FIG. 2

Values of the iodine coefficient, m_I, from different regions in scans of the abdomen in one patient following injection of contrast material.

scanning at 87 kVp and 140 kVp. These errors may be reduced by correcting the projection data (*e.g.* Herman, 1979) or, alternatively, the raw dual-energy projection data may be used directly to reconstruct images of the water and calcium chloride or iodine coefficients by adapting the method of Marshall et al (1981). This, however, requires access to the raw projection data.

For integration over small areas of the image, the error increased due to photon noise resulting from the finite number of X-ray photons detected per image. The precise error due to photon noise must be calculated with a knowledge of the noise power spectrum of the scanner and is dependent on size and shape of the averaging region (Riederer et al, 1978; Hawkes, 1982). A full description of the technique is not relevant here. The standard deviation of the Hounsfield numbers from a scan of a water phantom of 320 mm diameter, reconstructed onto a 320 × 320 matrix, was ±21.4 at 87 kVp and ±9.9 at 140 kVp. These errors are predominantly due to photon noise on the projections. For circular averaging areas of 192 pixels the standard deviation of the average Hounsfield numbers was calculated to be only ±0.9 at 87 kVp and ±0.4 at 140 kVp. These figures are considerably lower than the standard errors of the mean, due to the correlation between the Hounsfield numbers of adjacent pixels.

The final error in the Hounsfield number, quoted in the clinical results below, was found by combining in quadrature an error of 2 HU with the error due to photon noise.

For averaging areas larger than about 200 pixels ($200\ \mathrm{mm}^2$ in the CT slice) at least 10 mm from large areas of bone and avoiding visible artefacts, the standard deviations of the calcium chloride and iodine coefficients were found to be ±0.004 and $\pm 2 \times 10^{-4}$, respectively. Fat content, in units of kg/kg multiplied by the specific gravity of tissue, is equal to the calcium chloride coefficient divided by −0.0356 (from Table I). As adipose tissue has a specific gravity of approximately 0.92 (ICRP, 1975), fat concentrations of greater than 25% by weight may be detected with 95% confidence (two standard deviations). Defining bone mineral as 32.2% phosphorus and 67.7% calcium (ICRU, 1964), bone mineral content, in units of kg/kg multiplied by specific gravity, is equal to the calcium chloride coefficient divided by 1.1037 (from Table I). For averaging areas of 24 pixels ($24\ \mathrm{mm}^2$ in the CT slice) and neglecting beam-hardening errors, bone mineral content may be measured with a precision of ±0.01 (one standard deviation).

RESULTS

The results for four patients who had dual-energy scans are presented here to illustrate the technique. Three patients had examinations of the abdomen and one had a head scan. One of the patients who had a scan of the abdomen was scanned after the administration of contrast material. The scan of the head was performed both before and after the administration of contrast material. The contrast injection was 60 ml of Conray 420 (May & Baker Ltd), which is a solution of sodium iothalamate in water with an iodine concentration of 420 mg/ml.

The results of these scans are summarised in Figs 1–3. Figure 1 shows the calcium chloride coefficients for a variety of organs in scans of the abdomen of two patients, one with a cystic teratoma metastasis and the other with a solid teratoma metastasis, both subsequently confirmed at surgery. In these scans quantification of bone mineral content is possible. Figure 2 shows the results from the abdominal scan of the patient scanned after the administration of contrast material. In the iodine-enhanced scans of the abdomen there is an increase in the iodine coefficient within the aorta and vena cava compared with back muscle. Liver has a slightly elevated value of the iodine coefficient while fat has, as expected, a negative value of the iodine coefficient. The results from both Fig. 1 and Fig. 2 show good separation between fatty and non-fatty soft tissue. In the iodine-enhanced scan of the abdomen this permitted the identification of a suspicious low-density region of the liver as fat rather than metastasis or cyst, with a confidence of better than 99%.

Figure 3 shows the iodine coefficients from the scans of the brain before and after the injection of contrast material. There is, as expected, a significant increase in the iodine coefficient within the cerebral tumour. The

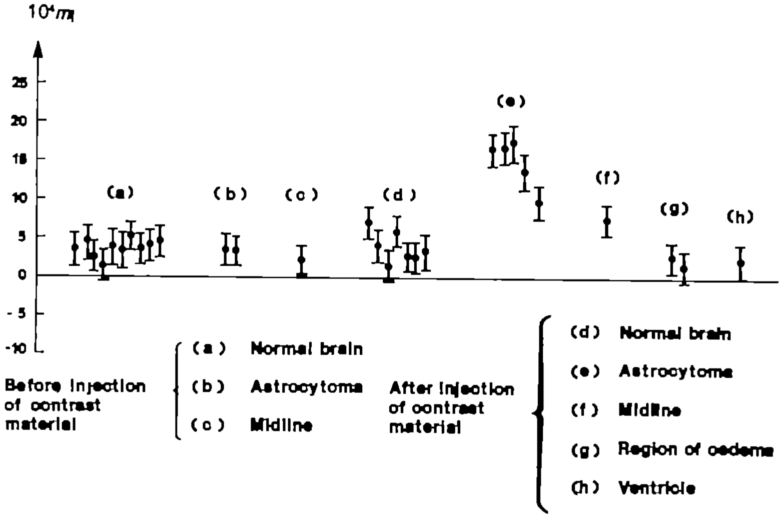

FIG. 3.

Values of the iodine coefficient, m_I, obtained from different regions in scans of the brain of one patient.

concentration of iodine is between 10^{-3} and 2×10^{-3} (in units of kg/kg multiplied by the specific gravity of tissue). The normal brain tissue shows no significant increase except in the midline.

CONCLUSIONS

The accuracy and, therefore, usefulness of dual-energy CT techniques has, so far, been limited due to errors in the Hounsfield numbers and due to incorrect formulation of the attenuation coefficient. We have presented a method of calibration and computation which is both simple to perform and eliminates errors in the parametrisation of the X-ray attenuation coefficient. This technique may prove useful in, for example:

(a) the measurement of bone mineral in all regions of the skeleton;
(b) separation of regions of fat or fatty infiltration from liquefaction in low-density lesions;
(c) quantification of iodine concentration after the injection of contrast material for assessment of tumour vascularity;
(d) the synthesis of images of the X-ray attenuation coefficient for a single X-ray energy, *i.e.* "mono-energetic reconstructions" and the synthesis of images of electron density, which may be useful in radiotherapy treatment planning;
(e) separation of clotted blood and fibrosis from a tumour with calcification;
(f) measurement of abnormal concentrations of high Z elements, such as hepatic iron in haemachromatosis.

In many of these examples, tissues may be satisfactorily characterised using a CT scan at a single energy. However, an abnormally high (or low) Hounsfield number may arise from either abnormally high (or low) electron density or an increase in the concentration of elements with higher (or lower) atomic numbers. The dual-energy technique permits the separation of these two contributions.

In addition, dual-energy CT permits the quantitation of, for example, changes in fat or bone mineral content, independently of variations in tissue density. This is impossible using conventional, single-energy CT. Quantification may prove useful in longitudinal studies of response to therapy and for studies of disease processes.

For the measurement of iodine concentration an unenhanced scan is usually available. In the absence of patient or tissue movement, subtraction of the unenhanced image from the enhanced image would, after careful calibration, yield the iodine concentration in the tissue. In practice, however, several minutes elapse between the two scans. Preventing patient movement and ensuring a reproducible scan position may prove difficult. Our method permits the quantification of iodine concentration from a pair of dual-energy scans taken after the injection of contrast material.

In certain circumstances, the observation that tissue can be represented by only two reference materials may result in difficulties in interpretation (Riederer et al, 1981; Kouris et al, 1982; Jackson & Kouris, 1983). For example, the presence of mineral or iodine will tend to cancel the contribution of fat to the derived coefficients. However, useful conclusions may result from the comparison of the coefficients between the normal and an abnormal region of an image. In addition, such a comparison will lead to some cancellation of systematic errors.

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Prominent periportal echogenicity: its sonographic evaluation and its significance

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ABSTRACT

Prominent periportal echogenicity was detected during sonographic examination of patients suffering from recurrent pyogenic cholangitis, hepatocellular carcinoma and acute cholecystitis. To document the finding, 140 normal individuals were studied to establish a norm for the evaluation of the periportal echogenicity. The significance of this sonographic finding and its possible aetiology are discussed.

Sonography is a well recognised method of evaluation of patients with hepatobiliary problems. The common duct (normal or dilated) can be demonstrated in almost every patient with the use of real-time equipment. During the sonographic investigation of a large number of patients with a variety of hepatobiliary problems, we had come across some patients with prominent periportal echogenicity, mainly around the porta hepatis. A similar sonographic sign had previously been described in schistosomiasis, mainly as a subjective observation. The present study aims to document and define this echographic feature more precisely. A control group of normal patients has been studied for periportal echogenicity, to establish a norm for the evaluation of patients with the abnormal finding observed over the same period.

MATERIAL AND METHODS

Over a period of 2 months, patients referred for sonographic investigation of systems other than the hepatobiliary system were included in the control group, with the following selection criteria.

(1) No history of previous hepatobiliary disease or operation.
(2) No clinical or laboratory evidence of jaundice or pancreatic disease.
(3) No sonographic and/or radiographic evidence of gallstone, ductal stone or pancreatic disease.

The normal appearance and measurement of periportal echogenicity were established from the study of this control group. Over the same period, patients discovered to have prominent periportal echogenicity were noted. Their sonograms and pathology were reviewed.

In this study, all the sonograms were obtained by using a Picker Digital Sectorview real-time sector scanner, with a 3.5 MHz, 19 mm-diameter transducer. Patients were examined in both supine and right anterior oblique positions. The common duct was seen as a tubular structure anterior to the portal vein at the porta hepatis. Usually, the hepatic artery could be seen between the duct and the portal vein as a small, circular structure. All measurements were then made at this level.

All measurements were made with equipment settings such that no significant echoes appeared in the portal-vein lumen (Fig. 1).

The following measurements were obtained for each patient.

A = the thickness of the anterior wall of the common duct.
B = the combined thickness of the posterior wall of the common duct and the anterior wall of portal vein.
C = the thickness of the posterior wall of portal vein.
D = the diameter of the lumen of the common duct.

RESULTS

One hundred and forty patients satisfied the selection criteria for the control group. Table I summarises the upper limit, range and most frequent value for each measurement in the normal patients.

Patients who had measurements of A, B and C above the upper limits of the control group were considered to have abnormally prominent periportal echogenicity. The pathological condition of these patients and the range of measurements in each condition are shown in Table II.

ILLUSTRATIVE CASES

Case 1

A 68-year-old male presented with a 2-day history of right upper quadrant pain and vomiting. On admission he was febrile with raised WBC count of 15×10^9/l, SGOT, SGPT, alkaline phosphatase and bilirubin levels were also slightly elevated. Sonographic examination of the upper abdomen demonstrated non-shadowing stones at the common hepatic duct, which was dilated, measuring 12 mm in diameter. Prominent periportal echogenicity was present. The anterior wall of the common hepatic duct measured 5 mm (Fig. 2). Intrahepatic ducts were not dilated. The gallbladder lumen could not be identified. However, strong echoes with sonic shadowing were detected at the gallbladder fossa region. The sonographic diagnosis was gallstones plus recurrent pyogenic cholangitis in view of the ductal dilatation, non-shadowing ductal stones and prominent periportal echogenicity. Endoscopic retrograde cholangiographic findings supported the

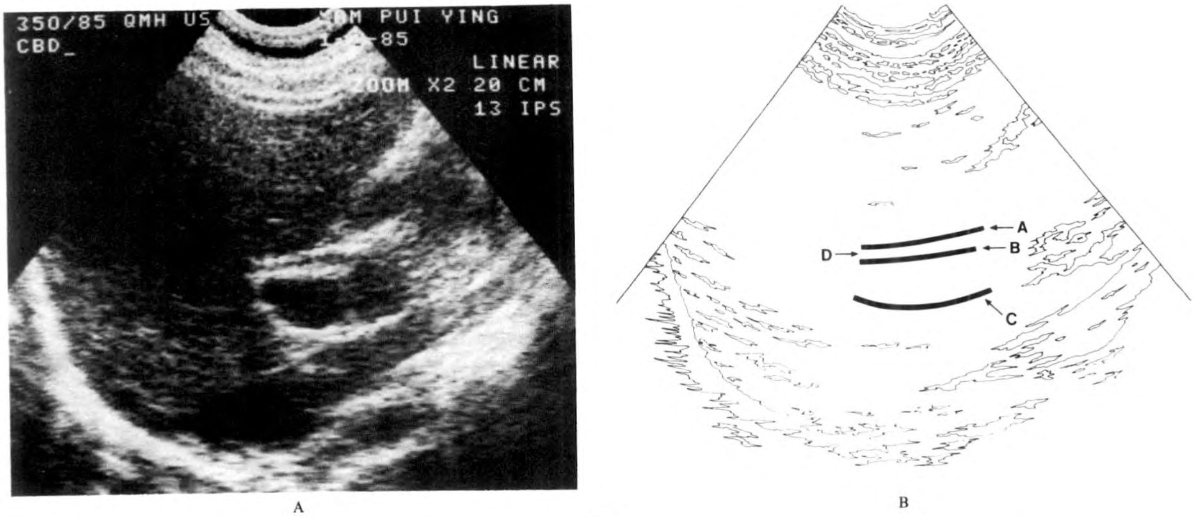


FIG. 1.

(A) Sagittal scan of a normal patient in the left posterior oblique position. The common duct was seen anterior to the portal vein. (B) Line drawing of (A) indicating how the measurements of A, B, C and D were made.

diagnosis of choledocholithiasis and recurrent pyogenic cholangitis. At surgery, the gallbladder was found to be contracted and contained stones. The common bile duct was dilated, containing stones, and the morphology was compatible with recurrent pyogenic cholangitis. The patient had a cholecystectomy and exploration of the common bile duct with removal of the ductal stones.

Case 2

A 49-year-old male had abdominal distension and marked weight loss. Hepatomegaly was discovered on physical examination and SGOT, SGPT, alkaline phosphatase and α-fetoprotein were raised. Sonographic examination revealed an irregular, echogenic mass in the right lobe of the liver. Tumour thrombus was found inside the portal vein and prominent periportal echogenicity was also present (Fig. 3). Angiography demonstrated a vascular tumour in the right lobe of the liver and tumour thrombus inside the portal vein, with tortuous vessels around it. Liver biopsy confirmed a hepatocellular carcinoma.

TABLE I

SUMMARY OF THE UPPER LIMIT, RANGE AND MOST FREQUENT VALUES FOR MEASUREMENTS A, B, C AND D

	A	B	C	D
Range (mm)	1–3	1–3	1–3	1–5
Maximum (mm)	3	3	3	5
Mode (mm)	1	2	1	2

TABLE II

RANGE OF MEASUREMENTS FOR A, B, C AND D IN VARIOUS PATHOLOGICAL CONDITIONS

Pathology	No. of patients	Measurements (mm)			
		A	B	C	D
Recurrent pyogenic cholangitis	10	5–14	2–8	1–3	8–29
Carcinoma of liver	4	1– 7	4–5	5–6	1– 5
Acute cholecystitis	1	6	6	2	5

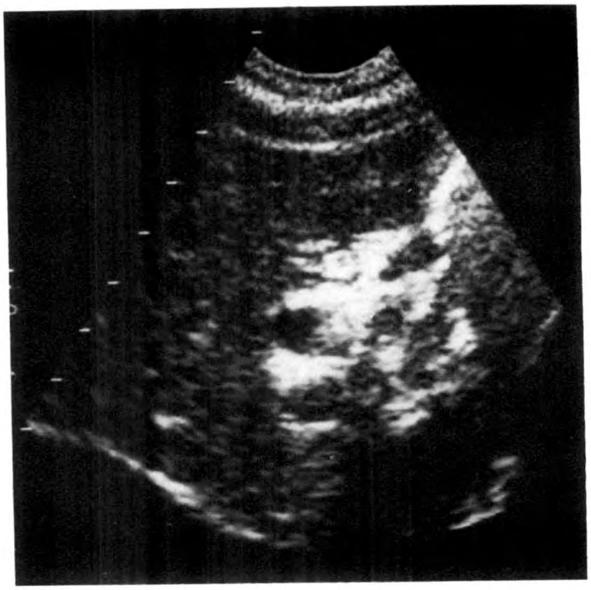


FIG. 2. *Case 1.*

Recurrent pyogenic cholangitis. Sagittal scan showing stones inside the common duct and the prominent periportal echogenicity.

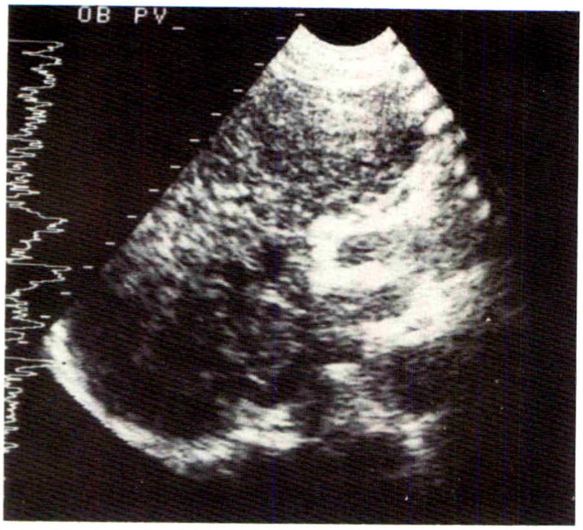


FIG. 3. *Case 2.*

Hepatocellular carcinoma. Sagittal scan showing the prominent periportal echogenicity. Tumour thrombus was also demonstrated in the portal vein.

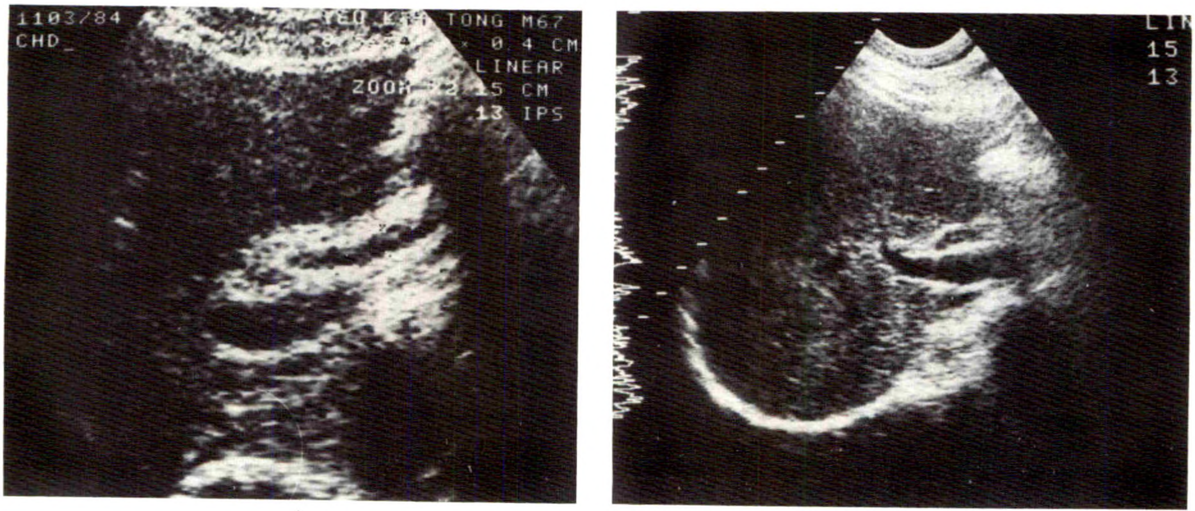
Case 3

A 67-year-old male presented with a 1-day history of right upper quadrant pain. On admission, he was afebrile, WBC count was slightly raised and bilirubin, SGPT and alkaline phosphatase levels were within normal limits. Sonographic examination showed prominent periportal echogenicity around the common hepatic duct, which was normal in calibre (Fig. 4A). The anterior wall of the common duct measured 6 mm. An area of high echogenicity with stone shadowing was seen at the gallbladder fossa, suggestive of contracted gallbladder with calculi. At surgery, a contracted gallbladder containing calculi was removed. The common bile duct was normal morphologically as well as on the operative cholangiogram. The patient was followed up sonographically 3 months later. The prominent periportal echogenicity had disappeared (Fig. 4B).

DISCUSSION

In schistosomiasis, prominent periportal echogenicity is a characteristic echographic feature (Cerri et al, 1984; Hussain et al, 1984). This is attributed to the periportal fibrosis which most commonly affects the porta hepatis. The whole wall of the portal vein appears to be thickened in this condition. The presence of this echographic feature is suggested as one of the main criteria for the diagnosis of this condition by Cerri et al (1984) and is considered pathognomonic by Hussain et al (1984). We have, however, observed similar sonographic features in other hepatobiliary conditions.

Recurrent pyogenic cholangitis, also known as oriental cholangiohepatitis or primary cholangitis, is a condition prevalent in Hong Kong and other parts of south-east Asia. It is characterised by repetitive episodes of cholangitis with fever, chills, epigastric or right upper quadrant pain and jaundice (Ong, 1962; Stock & Fung, 1962). It is the third most common cause of acute abdominal disorder in Hong Kong. Histologically, there is an increase in fibrous tissue in the portal tracts, especially around the bile ducts and portal radicles. The extrahepatic and intrahepatic ducts frequently show dilatation and stricture and may contain calculi, debris or, sometimes, frank pus. The calculi are composed almost entirely of bile pigment. Unlike gallstones, these calculi may not cast posterior acoustic shadowing and they may be less reflective. The aetiology of the disease remains obscure. The sonographic features of recurrent pyogenic cholangitis have



A

B

FIG. 4. *Case 3.*

(A) Sagittal scan showing the presence of prominent periportal echogenicity during the acute phase of cholecystitis. (B) Sagittal scan of the same patient 3 months later. Note the disappearance of the prominent periportal echogenicity.

been described (Ralls et al, 1981; Federle et al, 1982) but the finding of prominent periportal echogenicity was not mentioned. We have found it of sufficient frequency in occurrence to be included as one of the characteristic sonographic features in recurrent pyogenic cholangitis.

The prominent periportal echogenicity mainly affects the anterior wall of the common duct and, to a lesser degree, its posterior wall (Table II). This is in accordance with the pathology of recurrent pyogenic cholangitis, in which the fibrous tissue is found mainly around the bile ducts (Chou & Chan, 1980). However, this feature is not universally found in patients with longstanding recurrent pyogenic cholangitis with dilated common duct. It may be argued that such prominent periportal echogenicity may represent not the fibrous tissue but, rather, inflammatory tissue around the duct. More studies need to be done on this aspect and we are trying to elucidate the problem by following up some of these patients, with possible histological correlation.

Hepatocellular carcinoma is a common malignancy in Hong Kong. Arterioportal shunts are commonly found in this condition. Bookstein et al (1982) considered the main route of the flow to be transvasal and networks of large or small, tortuous vessels are frequently found near the hilus of the liver and at portal bifurcations in these patients (Cho & Lunderquist, 1983). These vessels appeared to be vasa vasorum supplying the tumours as well as the arterioportal shunt. Indeed, much of the apparent hypervascularity of hepatocellular carcinomas represents tortuous vasa, rather than tumour vessels themselves. The prominent periportal echogenicity found in this condition is probably due to these small vessels around the portal vein. In all four cases of hepatocellular carcinoma these vessels could be seen on the angiogram, supporting our speculation.

We have been able to detect prominent periportal echogenicity in one patient with typical findings of acute on chronic cholecystitis. It is a well known fact that the gallbladder wall may be thickened in patients with this condition (Marchal et al, 1978; Finberg & Birnholz, 1979; Mindele & Albert Ring, 1979). However, thickened common-duct wall has not been described in acute cholecystitis. The occurrence of this feature in Case 3 was a surprise to us, but retrospective review of our cases of acute cholecystitis has revealed a few more examples. Since the prominent periportal echogenicity was reversible, it may probably be reactive or inflammatory in nature. It may be that a similar pathogenesis to that in the gallbladder is operating at the porta hepatis region in this particular patient. We think that this must be a rare event.

In conclusion, prominent periportal echogenicity can be seen in a number of conditions and we have described it in recurrent pyogenic cholangitis, hepatocellular carcinoma and acute cholecystitis. It is also seen in hepatosplenic schistosomiasis. As more experience is gathered, more conditions may be found to have this sonographic feature, but much has to be done to clarify its pathogenesis. We believe that this feature can be due to a variety of causes, such as vessels and fibrous or inflammatory tissue. It is unlikely that a single cause is the sole reason for this sonographic appearance.

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Sarcoidosis of the parotid gland

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ABSTRACT

The clinical and radiological features of parotid-gland sarcoidosis in 22 patients are presented. This occurred in association with systemic disease as painless, diffuse and non-nodular parotid swelling. Conventional sialography usually demonstrated normal proximal ducts, a few fragile distal ducts and non-specific parenchymal nodules. Computed tomography, with or without simultaneous sialography, defined and characterised such nodules and demonstrated normal periparotid anatomy. Sialography contributes little additional information to thorough clinical examination in non-nodular or multinodular glands. However, solitary nodules appear to be better investigated by sialography, CT and CT-guided aspiration, thereby allowing diagnosis and direct medical therapy and avoiding surgery. Ultrasonography and nuclear scintigraphy were of little value in this study.

Parotid gland enlargement is a not uncommon clinical and radiological problem and the differential diagnosis can be tasking. In sarcoidosis, the parotid gland may be involved in up to 30% of cases (Hamner & Scofield, 1967). Parotid sialography (Schulz & Weisberger, 1947; Pfeiffer, 1963; Chisolm et al, 1971; Diamant, 1974) and computed tomography, with or without intraglandular contrast medium (Som et al, 1981a, b; Bryan et al, 1982), have been reported with variable findings and diverging conclusions in several small groups of patients with sarcoidosis. The experience with ultrasonography and nuclear scintigraphy in parotid swellings at our centre has been disappointing (Iko, 1984), although more favourable experiences with nuclear scintigraphy have been reported (Lauver & Gooneratne, 1979; Wiener & Patel, 1979; Blahd & Rose, 1981). In this paper we present and correlate the clinical and radiological features of parotid sarcoidosis in 22 patients, with emphasis on CT and sialography and in conjunction with other causes of parotid swelling seen over a 2-year period.

PATIENTS AND METHODS

All 22 patients were referred from one of our clinics or the Howard University Hospital (HUH) service at the District of Columbia General Hospital over a 2-year period.

Sarcoidosis was diagnosed on tissue specimens demonstrating non-caseating epithelioid granulomas in 21 cases prior to and in a single case following the study. There were 20 blacks, one Caucasian and one Mexican, consisting of 16 females and six males, age range 18–72, mean 34 years. A detailed clinical chart review was carried out and the parotid region evaluated on bimanual palpation. When nodules were palpated or suspected, conventional sialography preceded CT; when no nodules were palpable, CT without intraglandular contrast medium was performed. The precise details of the technique have been discussed recently (Iko, 1984). Briefly, the parotid ducts were analysed during the filling phase and the gland parenchyma during the excretory and emptying phases of sialography. Computed tomography was performed with or without intraglandular contrast medium using either an Ohio Nuclear whole-body scanner (with fast scan modification of 22 s) or, more recently, a GE CT/T 8800 scanner, to evaluate the parenchyma and adjacent structures and to characterise nodules. Two percutaneous CT-guided aspirations were performed.

Other procedures, namely ultrasonography and $^{99}Tc^{m}$ pertechnetate and ^{67}Ga citrate scans, were reviewed where available. Patient age and sex, duration and extent of extraparotid sarcoidosis and immunological and chemical parameters were tabulated and reviewed in relation to the radiographic features (Tables I and II) and possible effects of prednisone in those receiving it at the time of study. However, no attempt was made to correlate the clinical activity of disease, specific histological patterns, levels of serum angiotensin converting enzyme (SACE) or abnormal pulmonary function tests with the radiographic patterns. The illustrations were selected randomly.

RESULTS

Clinical

The majority of patients (Table I) were females (16, 72%); 15 (68%) were in the 20–40-year age group and 20 (91%) were blacks and of middle or, more commonly, low socio-economic status. Parotid gland sarcoidosis manifested as painless swelling in 21 cases (95%) and was painful in only one case (5%). It was acute, transient and self-limiting in 14 and chronic and persistent in eight. The enlargement was diffuse and non-nodular in 18 (82%), 12 of which were bilateral but

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TABLE I

Clinical data on 22 patients with parotid-gland sarcoidosis

Case	Age (years)	Sex	Duration of extraparotid disease (years)	Organs involved	Kveim-Siltzbach test	Tuberculin test	Elevated biochemical parameter
1	38	F	8	Chest II, spleen		−	Globulins
2	18	M	?	Chest II	+	−	Ca
3	28	F	6	Chest I, right submandibular gland	+		
4	32	M	12	Chest I	+	−	
5	48	F	8	Chest III, lymph nodes	+	−	
6	37	M	5.5	Chest III	+	−	Globulins
7	28	F	8.5	Chest II, eyes, CNS, facial nerve palsy	+		
8	22	M	5+	Chest II, eyes, nose	+	−	
9	38	F	6	Chest III, spleen	+		Ca
10	42	F	7	Chest II, spleen	+	−	Globulins
11	39	F	1.5	Skin, lymph nodes		−	
12	38	M	?	Thoracic II, skin		−	Ca
13	21	F	2	Chest I, skin		−	
14	42	F	6	Cervical lymph nodes, eyes	+		Globulins, Ca
15	42	M	4	Chest II, lymph nodes	+	−	
16	22	F		Chest I, skin, lymph nodes		−	Ca
17	32	F	6	Chest II, spleen, lymph nodes	+	−	Globulins
18	32	F	6	Chest II	+	−	Globulins
19	27	F	—	No extraparotid disease, one nodule right parotid	+		
20	72	F	10	Chest III, lymph nodes, bilateral multinodularity			Globulins
21	24	F	5+	Chest I, one unilateral nodule left			Ca
22	42	F	9	Chest II, skin, polyarthralgia, bone, multinodularity of left gland	+	−	Ca, Globulins

+positive, −negative.
Cases 1–12: diffuse bilateral non-nodular enlargement. Cases 13–18: diffuse unilateral non-nodular enlargement. Cases 19–22: nodular glands.

asymmetrical, while one or more nodules occurred in only four cases (18%). The mean duration of symptoms was 5 months (range 2 months–2 years) and the following associations were noted: simultaneous right submaxillary gland enlargement (one, 5%), xerostomia (seven, 32%), keratoconjunctivitis (three, 14%), elevated serum calcium (seven, 32%) and serum globulins (eight, 36%) and a negative tuberculin reaction (PPD) or a positive Kveim-Siltzbach (15, 68%).

Sarcoidosis was apparently limited to the parotid gland in only one patient (Case 19), who was also the only patient presenting with a painful swelling. The mean duration from onset of extraparotid sarcoidosis was 6.4 (range 0–12) years. The distribution was: chest, 19 (86%), with most patients in Stage II chest disease, according to a standard nomenclature (Siltzbach, 1976); lymph nodes, seven (32%); skin involvement, five (23%); spleen, four (19%); eyes, three (14%) and one (5%) each, bones and joints and the central nervous system. Other clinical findings included abnormal Shirmer test (semiquantitative test for tear production), pulmonary function and elevated SACE levels in a few cases.

Sialography

The indication for sialography was palpable or suspected nodules in eight cases, two of which were bilateral (Fig. 1). One additional submandibular sialogram was performed and demonstrated a nodule. The number, calibre and branching pattern of the opacified proximal ducts were within normal limits in eight of 11 sialograms. Main-branch ductal pathology, consisting of focal dilatation, spreading and displacement, occurred in only three nodular glands (Fig. 1). Minor duct features of acinar destruction, paraductal contrast

TABLE II

ANALYSIS OF RADIOLOGICAL FINDINGS AND CLINICAL DATA IN 22 CASES OF PAROTID SARCOIDOSIS

Findings	No. of patients	%
Diffuse, bilateral, non-nodular enlargement	12	55
Diffuse, unilateral, non-nodular enlargement	6	27
Nodular glands	4	18
Age (years)		
11–20	1	4.5
21–30	8	36
31–40	8	36
41–50	4	18
> 50	1	4.5
Duration of disease (years)		
< 1	1	4.5
1–5	4	18
6–10	14	64
> 10	1	4.5
Chest stage		
I	5	23
II	10	45
III	4	18
Lymph nodes	7	32
Spleen	4	18
Cutaneous	5	23
Ocular	3	14
CNS	1	4.5
Bones, joints	1	4.5
Kveim-Siltzbach, positive	15	68
Negative tuberculin	15	68
Elevated serum globulin	8	36
Elevated serum calcium	7	32

extravasations, so-called pseudosialectasis and displacements were seen in five cases (Fig. 1).

Computed tomographic sialography

This was performed on all of the eight patients subjected to parotid sialography. Enlargement was confirmed in all glands. The surrounding fat and fascial planes and the parotid fasciae were normal (Fig. 2). All palpable nodules were demonstrated. In only one of the five cases with suspected nodules was a nodule demonstrated; CT-guided aspiration yielded material on which a non-caseous granuloma was diagnosed. A subsequent Kveim-Siltzbach test was positive, while uveo-parotid fever, so-called Heerfordt's syndrome, developed 6 months later. All nodules were well demarcated and, on densitometry, were either the same or slightly decreased in density (Hounsfield units) compared with the normal parenchyma and/or the adjacent masseter muscle.

The nodules were bilateral and multiple in two patients (Fig. 3), unilateral and multiple in one and unilateral and single in one.

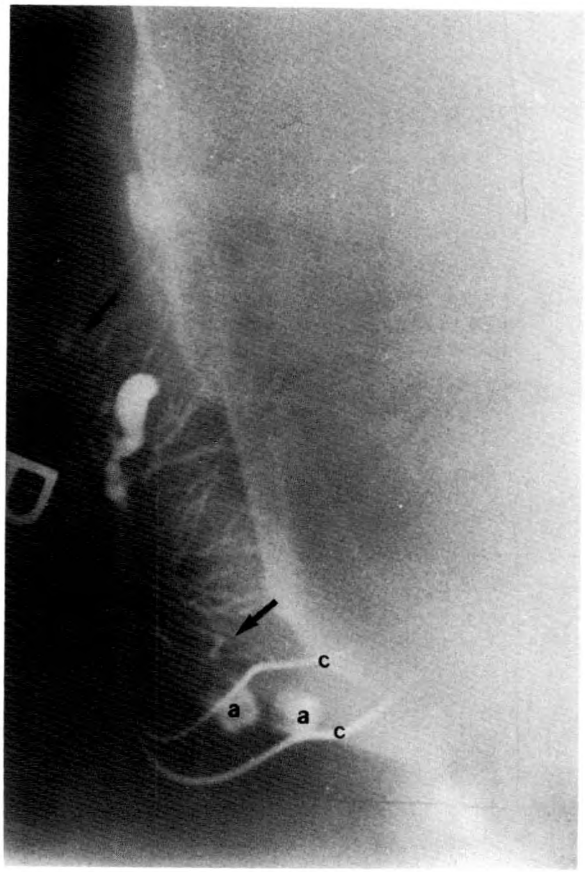

FIG. 1. *Case 20.*

Focal dilatation of the buccal portion of the right Stensen's duct (left normal), spreading of the second and distal order ducts and punctate paraductal extravasations (arrows). c, are catheters; a, artefacts.

Computed tomography without intraglandular contrast material

This was performed in 14 cases. Diffuse and non-nodular enlargement was bilateral (Fig. 4) or unilateral (Fig. 2). Including the four non-nodular CT-sialograms, there were 12 bilateral and six unilateral cases of diffuse enlargement. Periglandular anatomy was normal in every case.

Correlation of the clinical and radiographic profiles was limited by the sample size, the protean manifestations and the unpredictable clinical course of sarcoidosis (Table II). As a result, statistically meaningful data could not be generated. However, parotid nodules occurred only in females and appeared to increase with both patient age and the duration of the extraparotid disease. Response to prednisone therapy before or after the study showed no consistent pattern.

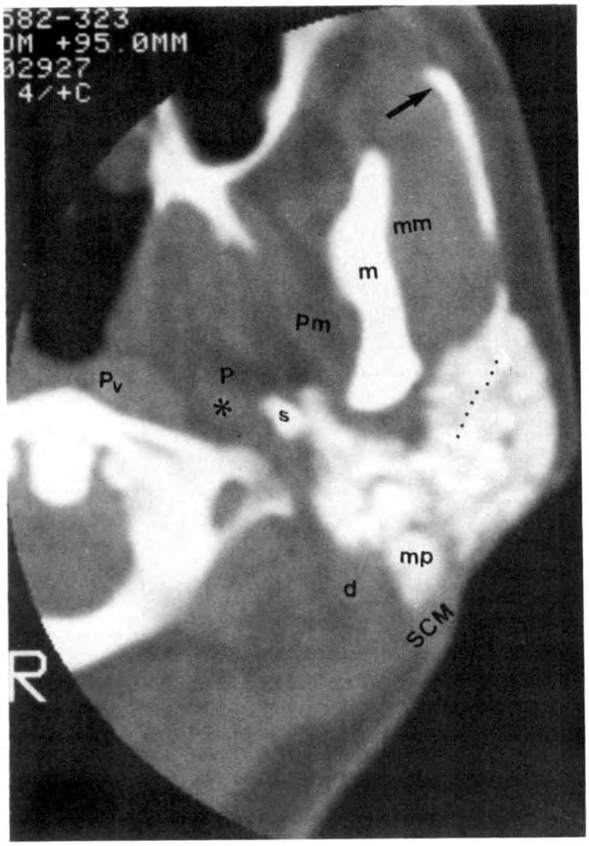

FIG. 2.

Computed tomographic sialogram in the transverse-axial plane through the left parotid gland (L+256, W 1200). Diffuse, non-nodular glandular enlargement and normal extra-organ anatomy and landmarks are well demonstrated: arrow, Stensen's duct; p, parapharyngeal space; d, digastric; Pm, pterygoid muscles; m, mandible; Pv, prevertebral muscles; mm, masseter; S, styloid process; mp, mastoid process; SCM, sternocleidomastoid. Dots indicate the approximate course of the facial nerve and * the carotid artery and jugular vein.

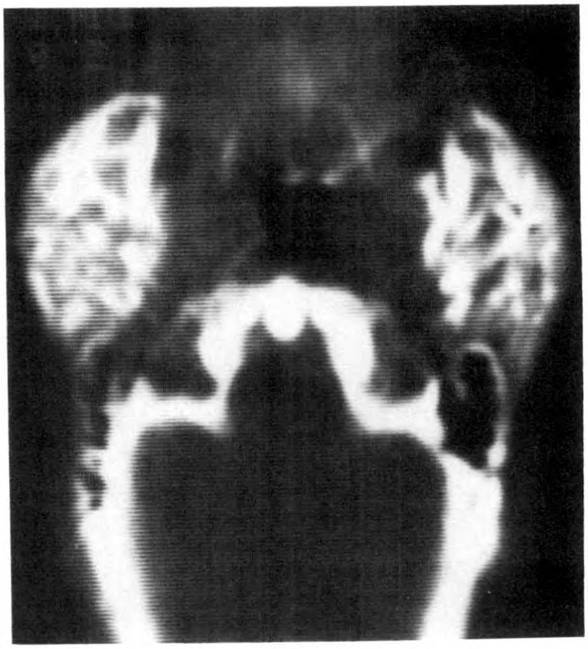

FIG. 3. *Case 20.*

Same patient as in Fig. 1. Coronal CT-sialograms demonstrating bilateral, multinodular parotids, but normal extraparotid relationships.

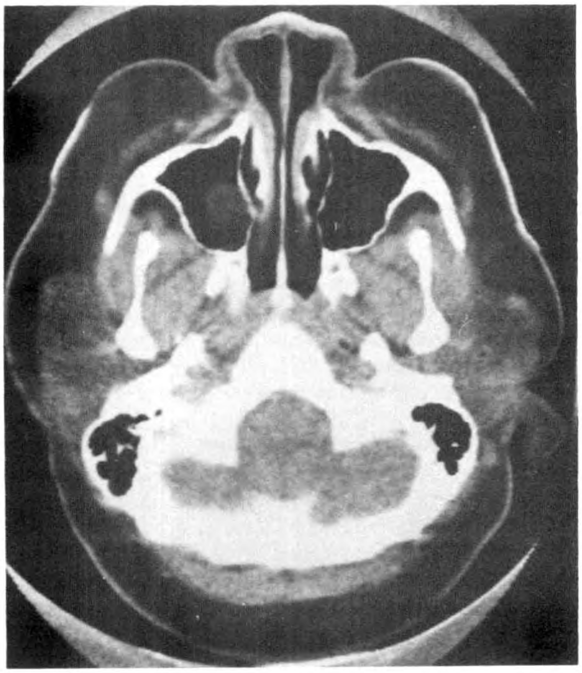

FIG. 4.

Transverse axial CT scan demonstrating diffuse, non-nodular, bilateral but asymmetrical enlargement with fatty replacement of glandular tissue.

Other investigations

Ultrasonography in four and pertechnetate scans in three patients contributed little useful information. Seven patients had non-specific ^{67}Ga scans. Percutaneous aspiration enabled the confirmation of a non-caseating granuloma in one case with established sarcoidosis and facilitated the diagnosis in another.

DISCUSSION

Sarcoidosis is a systemic disease characterised by non-caseating granulomas. Although a genetically primed autoimmune response (Warren, 1976) and a common aetiology with Sjögren's syndrome (Turiaf & Battesti, 1976) have been postulated, the aetiology remains undetermined. The parotid gland is enlarged in 6% (Greenberg et al, 1964) or in up to 30% (Hamner & Scofield, 1967). These figures suggest that parotid-gland sarcoidosis is sufficiently common to concern diagnostic radiologists and others in differentiating between the various types of salivary-gland enlargement.

Parotid-gland involvement occurred in association with sarcoidosis elsewhere, usually the chest, and after an average duration of 6.4 years. The common manifestation was painless swelling, often bilateral, asymmetrical and non-nodular. Sarcoidosis was apparently limited to the parotid gland and manifested as recurrent, painful swelling in one patient (Case 19) This was a 27-year-old Mexican female, very reminiscent of a previous case reported from Israel (Nitzan & Shteyer, 1982). Sialography and CT-sialography demonstrated an intraparotid nodule while CT-guided percutaneous fine-needle aspiration confirmed the diagnosis. Another unique association (Case 3) was that of bilateral, diffuse parotid enlargement with a nodule in the submandibular gland. Xerostomia was relatively common and suggests simultaneous minor salivary gland disease. Nodules were uncommon and, where present, were usually palpable. Most patients were blacks, probably reflecting the high concentration of blacks in the Washington DC area and the referral population at HUH. Of interest, however, is the predominance of females in the 3rd and 4th decades in our series, compared with another study reporting no significant difference but with males involved more in the 3rd and females more in the 4th decades (Greenberg et al, 1964). The patterns were acute, transient and self-limiting in 60% and chronic and persistent in 40%, while the response to steroid therapy was unpredictable Elevated serum calcium, abnormal globulins, positive Kveim-Siltzbach tests and negative tuberculin tests (PPD) were common features, consonant with earlier reports (Greenberg et al, 1964; Miglets et al, 1977).

Conventional sialography was often normal. Abnormal ducts were peripheral and associated with acinar destruction and pseudosialectasis. While non-specific, these latter features may reflect paraductal lymphocytic infiltration, granuloma or sclerosis and may relate to the volume of injected contrast material, pressure of injection and pre-existing ductal fragility. Previous reports on the sialography of parotid sarcoidosis range from consistently normal (Schulz & Weisberger, 1947; Suzuki & Kawashima, 1969; Chisolm et al, 1971, Som et al, 1981a), through "only slight changes" (Diamant, 1974), to "always abnormal" (Pfeiffer, 1963).

Computed tomography, with or without intra-glandular contrast injection, has been infrequently reported in this entity and we are aware of only about six previous cases from two sources (Som et al, 1981a, b; Bryan et al, 1982). It would seem that the radiological (*i.e.*, sialographic, CT-sialographic and CT) features relate to the duration and severity of the disease, to superimposed infection, to the limited tissue response of salivary tissue in general and to other, hitherto undefined parameters and variations in the natural history of sarcoid granulomas. Thus, via autoimmune mechanisms (Warren, 1976) or reactive and hormonal sialosis in systemic disease, an early phase with diffuse, perivascular inflammatory reaction or mononuclear-cell proliferation leads to a mature phase after which an even and concentric compression capsule develops, leading to a retrogressive phase. The latter occurs via the mechanisms of degeneration, simple atrophy and fibrosis (Barrie & Bogoch, 1953; Siltzbach, 1976). Thus, the radiological patterns may reflect any single phase of the natural history of the granulomatous process. Of some interest is the fact that the patient with the worst radiological appearances (Case 20, Figs 1, 3) had minimal clinical symptoms.

Our observations are at variance with previously published work. Som et al (1981a, b) reported five cases and consider a benign-appearing, multinodular gland to be the prototype. Race alone does not explain this disparity, since most patients in both series were blacks. Bryan et al (1982) studied 21 inflammatory parotid conditions on CT, one of which was sarcoidosis. They found no masses within the gland but they segregated sarcoidosis from Sjögren's syndrome, which demonstrated "irregular high and low densities". Distinction between sarcoidosis and Sjögren's syndrome may be specious (Warren, 1976) and, clearly, more work, possibly with controls, is needed.

The differential diagnosis on CT of diffuse parotid enlargement includes all granulomatous processes (Zeit, 1981). Parotid tumours are usually of increased density and may show signs of invasion; actinomycosis demonstrates both proximal and distal duct changes with cavitation and fistula formation (Iko et al, 1986), while major-branch ductal and periglandular involvement are characteristic of chronic pyogenic parotitis (Iko, 1984). Benign hypertrophy of the masseter may be confused with parotid-gland enlargement but the radiographic features in the former are distinctive (Dee, 1964). When nodules remain indeterminate on CT, diagnosis should be made by CT-guided percutaneous aspiration (Case 19) (Iko, 1984; Iko et al, 1986). Diamant (1974), reporting 12 such biopsies in sarcoidosis, states that "just in this lesion, this method is the method of choice" and it may spare patients diagnostic superficial parotidectomy.

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Measurement of total lung water from nuclear magnetic resonance images

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ABSTRACT

An accurate, non-invasive means of measuring pulmonary water is desirable, for both clinical and research use. Nuclear magnetic resonance imaging is theoretically very suitable for this purpose. Nuclear magnetic resonance (NMR) spectroscopy was used to show that the water content of lung tissue could be predicted accurately from the intensity of signal resulting from a 90° saturation recovery sequence. The water contained in an image section may, therefore, be calculated by reference to a 100% water standard. Lung water was obtained by imaging the lung in continuous sections and summing the water contents of the component sections. The method performed well when applied to a sponge phantom, but underestimated by up to 30% in excised sheep lung. The total (vascular and extravascular) pulmonary water measured by NMR in six healthy volunteers was 292 g (SD 58 g) or 4.6 g/kg body weight, less than predicted by some other indirect methods and post-mortem values. A briefer examination comprising two axial sections at standardised levels was also devised. In 15 healthy volunteers the mean water content of a 1.6 cm-thick axial section through the right lung was 17.8 g at the sternal angle, and 23.3 g 5 cm caudally. In the left lung, the values were 16.4 g and 16.3 g, respectively.

Pulmonary oedema can be a fatal consequence of a wide variety of severe cardiovascular, respiratory and multisystem disease. It is characterised by an increase in lung water content, the severity of which determines the degree of pulmonary dysfunction.

An accurate, non-invasive, readily repeatable means of measuring lung water is desirable both for the monitoring of treatment and as a research tool. Many methods have been devised, including various radiographic approaches (Pistolesi & Giuntini 1978; Snashall et al, 1981; Zetterstrom et al, 1984), computed tomography (Rosenblum et al, 1978; Wegener et al, 1978), Compton scatter techniques (Garnett et al, 1977; Gamsu et al, 1979), γ-ray attenuation (Simon et al, 1979), positron emission and transmission tomography (Ahluwalia et al, 1981; Rhodes et al, 1981), a radiometric method (Iskander et al, 1984), radioactive tracer techniques (Fazio et al, 1976) and non-radioactive indicator dilution methods (Lewis et al, 1979). None is ideal, however, as the continuing search for new techniques suggests.

The possibility of measuring lung water from NMR images is theoretically attractive. The NMR signal is derived from mobile protons in the region being examined and, since there is very little lipid in lung tissue, the source of this signal is mainly water.

An *in vitro* method of lung water measurement by nuclear magnetic resonance (NMR) imaging which uses a spin-echo pulse sequence has been published and the results obtained were encouraging (Hayes et al, 1982; Ailion et al, 1984; Cutillo et al, 1984).

This paper describes an NMR imaging method of lung water measurement and the results of its application to a phantom, excised sheep lungs and human volunteers.

METHOD

All images were obtained using the Aberdeen Mark II NMR imager, which employs a four-coil, air-cored resistive magnet producing a static magnetic field of 0.08 T. The NMR frequency for hydrogen protons is then 3.4 MHz. The Aberdeen spin-warp pulse sequence produces a spin echo every second. These are alternately known as the S_1 and S_2 echoes. The S_1 echo is obtained from a magnetic field gradient switching sequence preceded by a 90° radio-frequency pulse. This produces a signal which contains predominantly proton density (PD) information. The S_2 echo is obtained similarly, but the 90° pulse is preceded 200 ms earlier by a spin inversion achieved by adiabatic fast passage (AFP). This signal produces the inversion recovery image, containing both PD and T_1 information (Foster et al, 1984).

The data presented in this paper are derived purely from the proton density (S_1) images.

The data acquisition time for one section to be imaged by this pulse sequence is 4 min 16 s.

Total lung water

Six healthy volunteers, three male, three female (mean age 32 years, range 25–40 years), were imaged in the supine position. The thorax was imaged in the axial plane, starting at the level of the lung apices and moving caudally in 2 cm steps until the level of the diaphragm was reached. The image slice thickness was

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*F. M. MacLennan was the Research Fellow of the Association of Anaesthetists of Great Britain and Ireland during the period of the research.

2 cm. A bottle containing water doped with copper sulphate to yield a T_1 value of 220 ms was included in each section to act as a standard.

The lung water content was calculated as follows. The lung fields were outlined manually (excluding obvious hilar vessels) on the proton density images. The mean proton density and the number of pixels in the region of interest thus defined were calculated by the display program. At a slice width of 2 cm the approximate voxel size is 0.248 ml, enabling the volume of lung tissue in each image slice to be calculated. The ratio of the mean proton density of the water standard was multiplied by the lung slice volume to obtain the quantity of water in each lung slice. The volume and water content of each lung was obtained by summing the values obtained from all slices.

Sponge phantom

A rectangular plastic sponge was used to check the validity of the above method for calculating water content in an aerated material of low density. The sponge was enclosed in polythene to prevent evaporation, and contained known quantities of copper sulphate-doped water ($T_1 = 220$ ms). It was imaged along its length in 2 cm-thick sections, in the same manner as the volunteers' lungs. The experiment was performed five times with different quantities of water, to encompass the range of water density encountered in the volunteers. At the end of each experiment the first slice was imaged again to check that the water distribution had not altered under gravity. The sponge was also imaged when dry, to ensure that it was not the source of any signal.

Excised sheep lungs

Spectroscopy. In order to determine whether lung water content may be calculated from NMR signal intensity, pieces of freshly excised sheep lung were examined by NMR spectroscopy using a 90° pulse saturation recovery sequence with a repetition time of 1 s at 5 MHz.

The linearity of signal intensity from a Bruker CPX spectrometer to water mass was established. Eight sample tubes containing four different volumes of water and four specimens of H_2O/D_2O mixtures of different, known proportions were examined. All samples were doped to a T_1 of 175 ms.

Specimens of freshly excised sheep lung were similarly examined at repetition times of 1 and 2 s. The water content of the lung specimens was obtained by drying to constant weight at 80°C. Signal intensity was calibrated against the weight of water in the samples and a graph drawn. The predicted water content of the sheep lung specimens was obtained from the calibration graph and plotted against the water content obtained by drying.

Imaging. Four pairs of lungs were carefully excised from previously healthy sheep, killed, after stunning, by exsanguination. The lungs were, thus, relatively blood-free. In two instances the trachea was intubated and the lungs inflated to full inspiration with air. In the remaining two instances, the lungs were left in their partially inflated condition. They were placed in a plastic tray, covered with polythene to prevent evaporation and imaged throughout their length in 2 cm-thick sections. The bottle of copper sulphate-doped water ($T_1 = 220$ ms) was, again, included in each section. Lung volume remained constant throughout the imaging period. The water content was calculated from the images as previously described. After imaging, the lungs were minced, weighed and dried in a sand bath at 110°C to constant weight.

Standard section images from volunteers

Fifteen healthy volunteers (mean age 28 years, range 19–35 years) were imaged in the axial plane at two standard levels, *i.e.* at the sternal angle and 5 cm caudal to that. The slice thickness of these images was 1.6 cm, the default value of the imaging system.

The data from these images were processed in two different ways in order to characterise the features of normal proton density and slice water content. Firstly, the volume and water content of the right and left lung section were calculated at both levels and the water density (g/ml) derived. Secondly, the antero-posterior (AP) gradient of proton density with respect to the 100% water standard was determined. To achieve this a 1 cm-wide strip region of interest was drawn from the anterior edge to the posterior edge of the lung field, midway between the hilum and the lateral lung border of the right lung. (The left lung is frequently a crescent shape impossible to measure in this way.) This strip was divided into 1 cm squares (Fig. 1). The outermost 1 cm regions were discarded to avoid error introduced through partial-volume effect with adjacent chest wall. The mean proton density of the neighbouring 2 cm × 1 cm area was obtained at the anterior and posterior ends of the strip. Data from the centre of the strip were also discarded as it was frequently found to be variably biased by the presence of large pulmonary blood vessels. The values for mean proton density were converted to density with respect to 100% water by dividing by the proton density value of the water standard included in each image section. The ratio of posterior to anterior regions of interest was also calculated for both cranial and caudal sections, as an index of the AP gradient of lung water density.

RESULTS

Total lung water in volunteers by NMR imaging

The values of lung volume and lung water content obtained from NMR imaging are shown in Table I. The data have also been expressed as water density per unit lung volume measured and lung water/kg body weight.

Sponge phantom

True water content plotted against water content calculated from the NMR images is shown in Fig. 2.

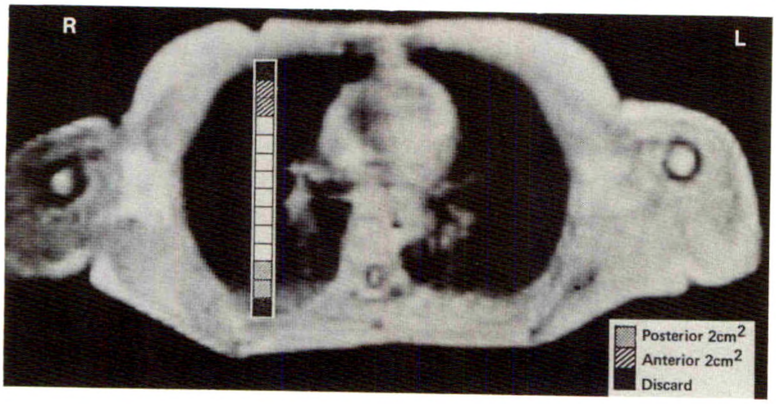

FIG. 1.

Axial section through the thorax. A region of interest 1 cm wide is positioned in the right lung for measurement of proton density.

The relationship is linear with correlation coefficient $r = 0.99$.

Sheep lungs

Spectroscopy. Figure 3 shows that NMR signal intensity is linearly related to mass of water ($r = 1$) both alone and as part of a D_2O/H_2O mixture. Nuclear magnetic resonance signal intensity is also linearly related to sheep lung water content. The predicted water content of the sheep lung is plotted against water content obtained by drying for the 1 s and 2 s pulse repetition experiments (Fig. 4).

TABLE I

MEASUREMENTS BY NMR IMAGING IN SIX HEALTHY VOLUNTEERS

	Lung	Total lung water (g)	Lung water (ml/kg body weight)	Volume (ml)	Water density (g/ml)
	Male				
	Right	195.4		1310.7	0.15
	Left	197.0		1160.0	0.17
	Total	392.4	5.2	2470.7	0.16
	Right	140.3		933.0	0.14
	Left	147.8		982.2	0.15
	Total	288.1	5.0	1915.2	0.15
	Right	109.6		674.6	0.16
	Left	107.9		518.0	0.21
	Total	217.6	3.6	1192.6	0.18
	Female				
	Right	161.1		1025.7	0.16
	Left	142.9		790.7	0.18
	Total	304.0	5.7	1816.4	0.17
	Right	151.5		881.6	0.17
	Left	134.3		691.1	0.19
	Total	285.8	3.5	1572.7	0.18
	Right	124.3		738.6	0.17
	Left	138.9		676.0	0.20
	Total	263.2	4.6	1414.6	0.19
Mean	Right	147.0	—	927.4	0.16
SD	Right	30.1	—	227.3	0.01
Mean	Left	144.8	—	803.0	0.18
SD	Left	29.1	—	232.2	0.02
Mean	Total	291.8	4.6	1730.4	0.17
SD	Total	57.7	0.89	448.0	0.01

Imaging. The values of total water content obtained by drying and by NMR imaging of each excised sheep lung are shown in Table II.

Standard section images from volunteers

Individual and mean values of water content, volume and water density of the two axial sections of each lung are displayed in Table III (level of plane is at the sternal angle) and Table IV (level of plane 5 cm caudal to the sternal angle).

Water density. The density of water in the left lung is greater than the right at both the sternal angle level ($p < 0.001$) and at the more caudal level ($p < 0.001$). Lung water density is consistently higher at the caudal level than the sternal angle for both right ($p < 0.001$) and left ($p < 0.001$) lungs.

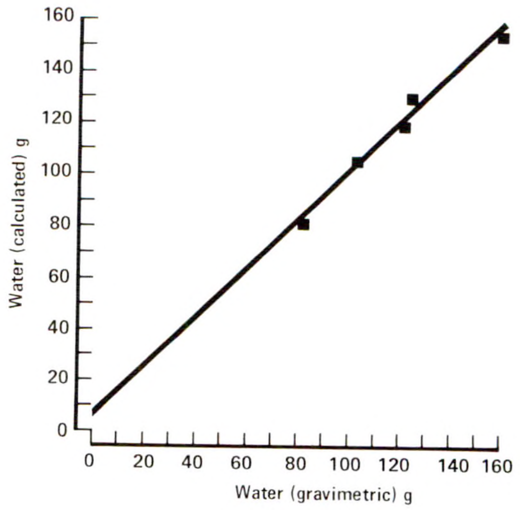

FIG. 2.

Sponge phantom. Correlation between NMR-derived and gravimetric values of water content (correlation coefficient $r = 0.99$).

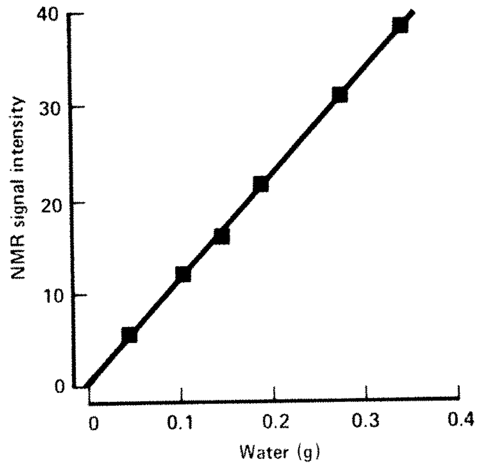

Fig. 3.

NMR spectroscopy at 5 MHz (90° saturation recovery). Calibration of signal intensity by water standards (correlation coefficient $r = 1.0$).

Water content. The water content of the right lung section is greater than the left at both the sternal angle level ($p < 0.05$) and at the more caudal level ($p < 0.001$). In the right lung, the water content of the caudal section is greater than the sternal angle section ($p < 0.001$), but the water content of the left lung is not significantly different at the two levels.

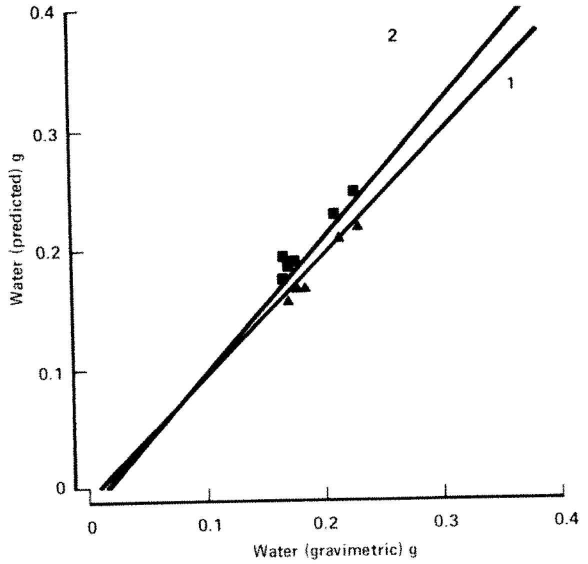

Fig. 4.

NMR spectroscopy at 5 MHz (90° saturation recovery). NMR-predicted water content plotted against gravimetric water content of excised sheep lung. ▲ pulse repetition time = 1 s ($r = 0.99$); ■ pulse repetition time = 2 s ($r = 1.0$).

TABLE II

Excised sheep lung measurements

Water content by drying (g)	Water content from NMR image (g)	% water detected by NMR
Semi-collapsed lungs		
311	217	70
412	342	83
Fully inflated lungs		
290	233	80
269	217	81

Volume. The slice volume is greater on the right side than the left at both scan levels ($p < 0.001$). On the right side the more caudal section is larger than the sternal angle section ($p < 0.001$). The situation is reversed on the left side, however, the sternal angle section being larger than the more caudal section ($p < 0.001$). The results are summarised in histogram form in Fig. 5.

The proton density of standard anterior and posterior regions of a 1 cm wide region of interest positioned vertically down the right lung was standardised by dividing by the proton density of water imaged simultaneously. These standardised proton densities and their posterior : anterior ratios are shown in Tables V and VI.

The values obtained from the posterior region are always greater than those from the anterior region, both at the level of the sternal angle ($p < 0.001$) and 5 cm caudally ($p < 0.001$). There is, however, no significant difference between the anterior : posterior ratios at the two levels ($p < 0.5$).

These results were compared using Student's t-test for paired observations.

Discussion

The method of lung water measurement described above depends fundamentally on two things: that the intensity of the NMR signal is proportional to the mass of water which produces it and that the water content of lung tissue can be predicted accurately from signal intensity. Both of these points were established by NMR spectroscopy. Reduction of the interpulse interval from 2 s to 1 s did not affect linearity, but there was a 10% decrease in signal size, implying that some saturation of the tissue signal had occurred at the faster pulse rate.

Normal lung tissue produces a rather small NMR signal and so the sponge model was used to test the performance of the basic method and calculation in an aerated material of similarly low density. There was excellent agreement between the calculated and actual water content. When the imaging experiment was repeated with whole excised sheep lungs, however, there was a considerable discrepancy between the calculated water content and that obtained by drying. A 10%

TABLE III

MEASUREMENTS ON 1.6 MM-THICK AXIAL SECTIONS THROUGH THE RIGHT AND LEFT LUNGS OF 15 HEALTHY VOLUNTEERS AT THE LEVEL OF THE STERNAL ANGLE

	Right lung			Left lung		
	Volume (ml)	Water content (g)	Water density (g/ml)	Volume (ml)	Water content (g)	Water density (g/ml)
	102.6	16.8	0.16	101.8	18.3	0.18
	138.2	15.5	0.11	110.0	13.8	0.12
	112.8	19.4	0.17	87.7	17.4	0.20
	118.8	17.3	0.14	89.9	14.0	0.16
	118.4	23.7	0.20	98.4	22.0	0.22
	139.3	19.0	0.14	103.4	17.0	0.16
	117.6	15.3	0.13	94.5	15.5	0.16
	107.7	18.4	0.17	105.7	19.8	0.19
	122.3	21.1	0.17	85.9	15.3	0.18
	128.5	16.6	0.13	90.3	14.0	0.15
	143.0	21.1	0.15	101.0	15.6	0.15
	119.6	17.1	0.14	87.9	14.6	0.17
	89.7	12.0	0.13	91.9	14.4	0.16
	162.2	18.8	0.12	126.1	18.4	0.15
	126.1	15.3	0.12	104.1	16.1	0.15
Mean	123.1	17.8	0.15	98.6	16.4	0.17
SD	17.8	2.9	0.02	10.7	2.4	0.02

signal loss was expected as a consequence of partial saturation, since the interpulse interval on the imager is fixed at 1 s, but the outstanding 7–20% deficit was puzzling. An explanation may lie in the recently published work of Morris et al (1985). They have shown that the T_2 of lung tissue is shortened when the lung is inflated, as a result of local field inhomogeneities caused by the many gas/water interfaces. This effect might result in significant loss when using the Aberdeen saturation recovery sequence.

Evaluation of the results obtained from healthy volunteers is not straightforward. Comparison must be

TABLE IV

MEASUREMENTS ON 1.6 MM-THICK AXIAL SECTIONS THROUGH THE RIGHT AND LEFT LUNGS OF 15 HEALTHY VOLUNTEERS AT A LEVEL 5 CM CAUDAL TO THE STERNAL ANGLE

	Right lung			Left lung		
	Volume (ml)	Water content (g)	Water density (g/ml)	Volume (ml)	Water content (g)	Water density (g/ml)
	130.9	25.2	0.19	77.2	17.3	0.22
	154.2	21.9	0.14	109.7	19.7	0.18
	106.3	18.1	0.17	76.8	15.1	0.20
	130.3	22.2	0.17	96.0	16.4	0.17
	144.5	28.9	0.20	60.6	14.7	0.24
	183.1	27.5	0.15	98.6	19.9	0.20
	143.9	20.9	0.14	61.6	11.8	0.19
	128.3	21.7	0.17	61.4	13.1	0.21
	115.1	21.6	0.19	82.8	18.6	0.22
	136.6	19.7	0.14	83.4	13.4	0.16
	162.7	29.3	0.18	109.1	23.3	0.21
	146.5	21.4	0.15	68.1	15.7	0.23
	150.3	26.1	0.17	90.2	18.0	0.20
	196.6	26.6	0.13	91.5	16.9	0.18
	146.3	17.9	0.12	62.7	10.6	0.17
Mean	145.0	23.3	0.16	82.0	16.3	0.19
SD	23.4	3.7	0.02	17.0	3.3	0.02

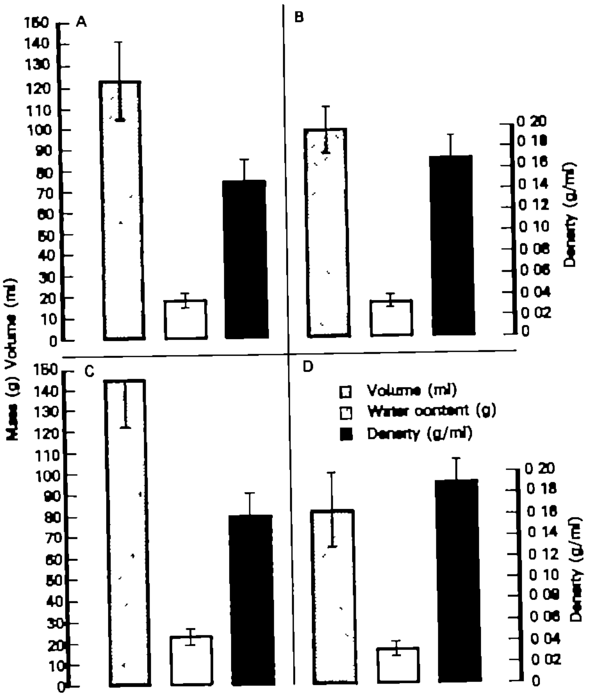

FIG. 5.

Histogram to show mean (±1 SD) of the water content (g), volume (ml) and density (g/ml) of a 1 6 cm-thick axial section through right and left lungs at the level of the sternal angle and 5 cm caudally to the sternal angle. (A) right lung, sternal angle level; (B) left lung, sternal angle level; (C) right lung, 5 cm caudal to sternal angle, (D) left lung, 5 cm caudal to sternal angle.

TABLE V

PROTON DENSITY OF LUNG, RELATED TO THE PROTON DENSITY OBTAINED FOR 100% WATER. ANTERIOR AND POSTERIOR REGIONS OF A 1 CM-WIDE REGION OF INTEREST THROUGH AN AXIAL IMAGE OF THE RIGHT LUNG AT THE LEVEL OF THE STERNAL ANGLE IN 15 HEALTHY VOLUNTEERS

	Anterior	Posterior	Posterior. anterior ratio
	0.14	0.16	1.1
	0.08	0.11	1.4
	0.11	0.17	1.5
	0 13	0.18	1.4
	0.12	0.25	2.0
	0.11	0.14	1.3
	0 16	0.21	1.3
	0.11	0.16	1.4
	0.14	0.19	1.4
	0.09	0.14	1.5
	0.10	0.15	1.5
	0.09	0.17	1.9
	0.09	0.14	1.5
	0.11	0.11	1.0
	0.08	0.13	1.6
Mean	0.11	0.16	1.45
SD	0.024	0.037	0.26

made with values obtained either at post-mortem, or by other indirect methods of lung water measurement. Post-mortem lung weight and water content are heavily influenced by the mode of death, the time elapsed between death and lung excision and to what degree the lungs are drained of blood before weighing (Durlacher et al, 1950).

Our method measures total lung water and is unable to distinguish the vascular from the extravascular contribution. Large blood vessels were, however, deliberately excluded from the measurement.

A value of 543 g has been reported for the total (vascular and extravascular) water content of normal lungs at post-mortem examination (Staub, 1974). This is considerably higher than the mean value obtained in this study (292 g). Various indicator dilution methods which measure extravascular lung water only have resulted in a range of values including 2.16 ml/kg (Goresky et al, 1975), 5.5 ml/kg (Pistolesi & Giuntini, 1978) and 5.7 ml/kg (Lewis et al, 1979), although a recent report indicates that this last method overestimates lung water (Fallon et al, 1985). When the NMR total lung water values are similarly corrected for body weight, a mean value of 4.6 g/kg (±0.89) is obtained, again suggesting that our method underestimates lung water.

Some of the reasons for this underestimation are obvious. A signal reduction of approximately 10% was

TABLE VI

PROTON DENSITY OF LUNG, RELATED TO THE PROTON DENSITY OBTAINED FOR 100% WATER. ANTERIOR AND POSTERIOR REGIONS OF A 1 CM-WIDE REGION OF INTEREST THROUGH AN AXIAL IMAGE OF THE RIGHT LUNG AT A LEVEL 5 CM BELOW THE STERNAL ANGLE IN 15 HEALTHY VOLUNTEERS

	Anterior	Posterior	Posterior: anterior ratio
	0.14	0.24	1.7
	0.10	0.16	1.6
	0.13	0.17	1.2
	0 13	0.16	1.2
	0.18	0 24	1.3
	0.10	0.16	1.6
	0.12	0.22	1 8
	0.10	0.19	1.9
	0.14	0.19	1.3
	0.10	0.18	1.8
	0 11	0.17	1.5
	0.09	0.14	1.5
	0.10	0.19	1.9
	0.09	0.15	1.7
	0 08	0.15	1.9
Mean	0.11	0 18	1.59
SD	0.026	0.031	0.25

expected due to partial saturation. The partial volume effect, common to all tomographic techniques, inevitably causes some lung tissue to be lost around the lung edges. The effect of this may be minimised by imaging in thinner slices, but the consequently prolonged examination time and smaller signal size limit the usefulness of this manoeuvre. Respiratory movement must also be responsible for some loss of data, particularly at the lung bases.

Blood flow is not expected to be a major source of error since one of the features of the Aberdeen Mark II imager is its relative insensitivity to flow effects (Hutchison & Smith, 1981). A much wider area is excited than actually imaged, so that blood has a high intensity on the proton density image even when flowing rapidly through the section.

The time required for whole lung imaging is 45–60 min, which may be intolerably long for a dyspnoeic patient to remain supine. The two-slice examination was devised as a quicker alternative to total lung water measurement in the compromised patient.

The water content of an axial lung section is much less affected by lung volume than is the density of that section. Expansion in the axial plane will considerably reduce the water density, although the water content will remain the same. Expansion of the lung in the longitudinal plane, however, will diminish the actual section water content to some extent.

Lung density is only useful as an index of lung water if volume is also known, or at least standardised, lung inflation being a very important determinant of lung density. Figure 5 illustrates how misinterpretation may occur if density values are viewed in isolation; the density of the left lung sections is greater than the right at both levels, but in fact the water content of the right sections is greater than the left.

The proton density measurements from within the right lung show the expected increase in lung water density posteriorly. This effect has been shown to be predominantly due to greater perfusion of the dependent regions of the lung, extravascular water being more evenly distributed (Rhodes et al, 1981).

The clinical value of the two standard axial lung sections remains to be established. A trial is presently in progress whose aim is to evaluate the examination in a group of patients with cardiovascular disease.

This paper describes one method of measuring lung water with NMR imaging. The specification of the imager, the method of image reconstruction, the pulse sequence employed and the display software all place constraints on the approach which can be taken. The images of thorax described by Gamsu et al (1983), for example, are quite different from the Aberdeen images, having no signal from flowing blood. Where this is the case, it may be possible to measure extravascular lung water directly.

The Aberdeen method of lung water measurement is simple in principle. It requires only the inclusion of a water bottle in the section to standardise the S_1 signal and correct for any drift. It is, however, rather cumbersome in imaging and calculation time. Nuclear magnetic resonance imaging technology is developing rapidly and features such as simultaneous multislice imaging and respiratory gating should both reduce the examination time and increase its accuracy. The development of image display software dedicated to the calculation of lung water from the images would reduce the calculation time.

At present, this method is unable to distinguish vascular from extravascular water. The solution to this difficult problem may lie in identifying the vascular component by means of its flow or relaxation characteristics, or by the use of suitable contrast agents. Much work remains to be done if this use of NMR imaging is to achieve its full potential.

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Magnetic resonance imaging and hydatidiform mole

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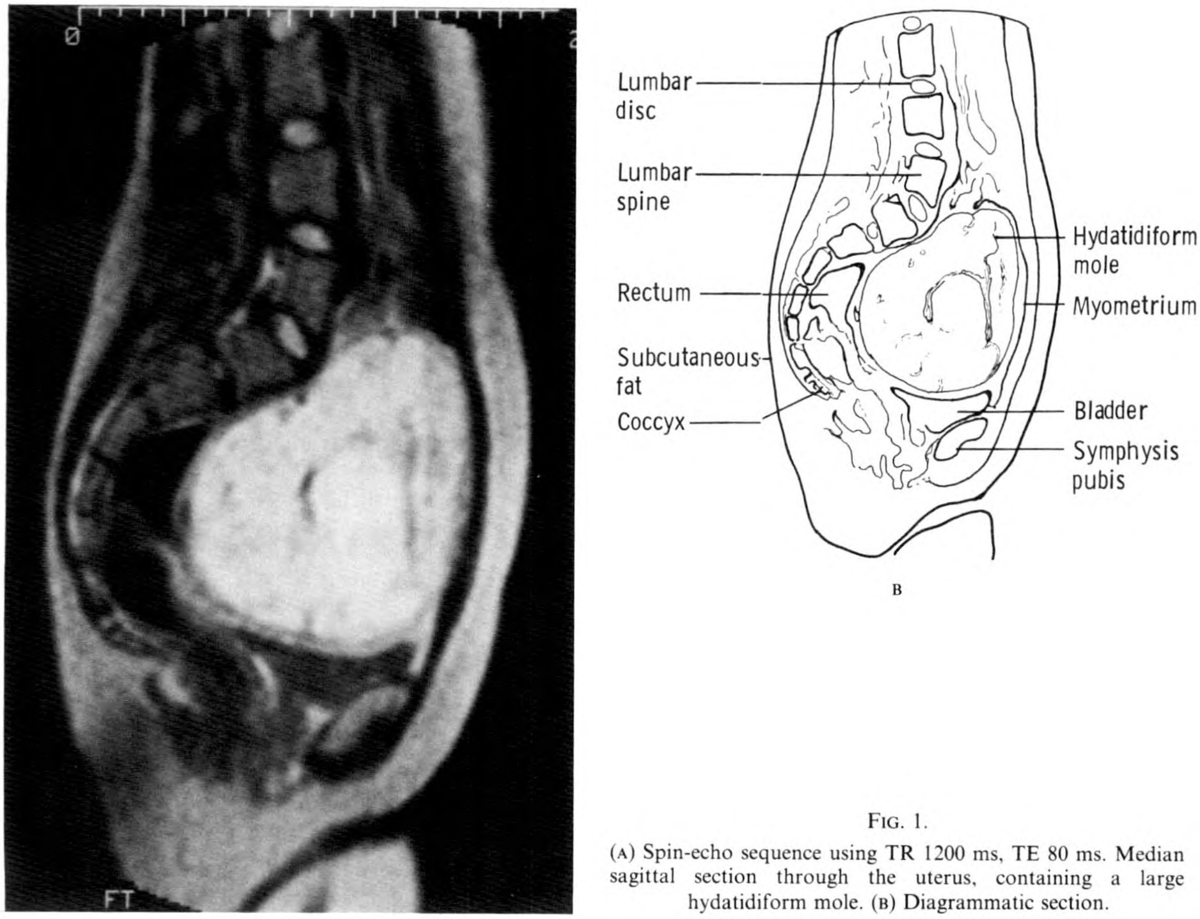
ABSTRACT

Five women with complete and partial hydatidiform mole were examined by magnetic resonance imaging (MRI). Spin-echo pulse sequences (T_2 weighted) were found to provide excellent resolution, while inversion-recovery pulse sequences (T_1 weighted) gave better pathological detail. The myometrium was clearly seen on each patient and no invasion by the tumour detected. This corresponded to the histological findings. The potential uses of magnetic resonance in the diagnosis of primary and recurrent trophoblastic disease and its role in management are discussed.

Malignant trophoblastic disease is an infrequent complication of gestation occurring in one in 2000 pregnancies in this country (Hammond et al, 1978). Trophoblastic neoplasia falls into the category of human disease where little is known about the cause, whilst the diagnosis and management have developed to a point where morbidity is low and mortality is rare. The mainstay of diagnosis is ultrasound (Leopold, 1971) and it was MacVicar and Donald (1963) who were the first to describe the characteristic speckling seen with hydatidiform mole. Magnetic resonance represents a new method of imaging which produces



A

B

FIG. 1.

(A) Spin-echo sequence using TR 1200 ms, TE 80 ms. Median sagittal section through the uterus, containing a large hydatidiform mole. (B) Diagrammatic section.

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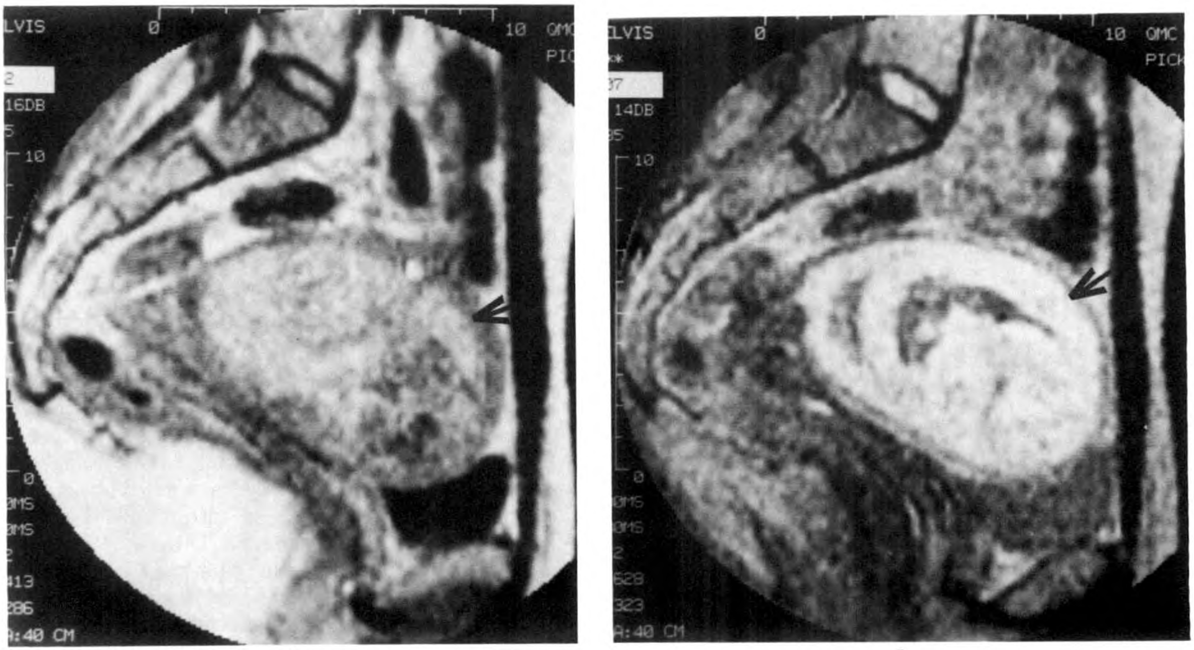

A

B

FIG. 2.

Median sagittal sections of a hydatidiform mole (arrow) on spin-echo sequences: (A) TR 760 ms, TE 40 ms; (B) TR 1500 ms, TE 80 ms.

cross-sectional images of the body which reflect the distribution density of protons and parameters relating to their motion (T_1 and T_2 relaxation times) in cellular water and lipids. As with CT and ultrasound, the display of soft-tissue anatomy is at a premium. Magnetic resonance imaging has the advantages of imaging in any plane, avoiding the use of ionising radiation and, when used appropriately, is not associated with any known biological hazard. By altering the pattern of radio-frequency radiation applied to the pulse sequences, images can be produced weighted differently by proton density and the relaxation times T_1 and T_2. The paper details our initial experience with magnetic resonance and gestational trophoblastic neoplasia.

MATERIALS AND METHODS

Five women with clinically suspected trophoblastic disease were examined by MRI at the University Hospital, Nottingham. All patients had ultrasound examinations prior to MRI. The MRI scans were performed on a Picker 0.15 T imaging system based on a resistive magnet. The sequences we have found to be of most value were an inversion-recovery sequence with a TR of 2000 ms and TI of 600 ms and spin-echo sequences with a TR of 2000 ms with a variable TE. The TE_{40} sequence provides good anatomical definition but the TE_{80}, like the IR_{600} sequence, provided more pathological information. A combination of sagittal, coronal and transverse views was obtained in each case.

RESULTS

In each of the five cases examined, MRI correctly diagnosed the presence of molar tissue. Subsequent histological examination confirmed the diagnosis of hydatidiform mole in all, with no invasion of the myometrium.

In Fig. 1 a median sagittal scan of a patient with a large mole is shown. The uterus is enlarged and distended with molar tissue, which is seen to give a high signal with this particular spin-echo sequence (TR 1200 ms, TE 80 ms). A rim of myometrium is observed around the molar tissue demonstrating no evidence of invasion, correlating with the histological findings. The vesicular nature of hydatidiform mole can also be seen. Molar tissue yields a high signal when using spin-echo sequences with a long TE.

In Fig. 2 the effect of altering the TR and TE of a spin-echo sequence is shown in another patient. Figure 2A is a median sagittal scan through the uterus; the distinction between molar tissue and the myometrium with this sequence is lost and the internal structure indistinct (TR 760 ms, TE 40 ms). In Fig. 2B the same image is shown with a different spin-echo sequence taken in the same plane (TR 1500 ms, TE

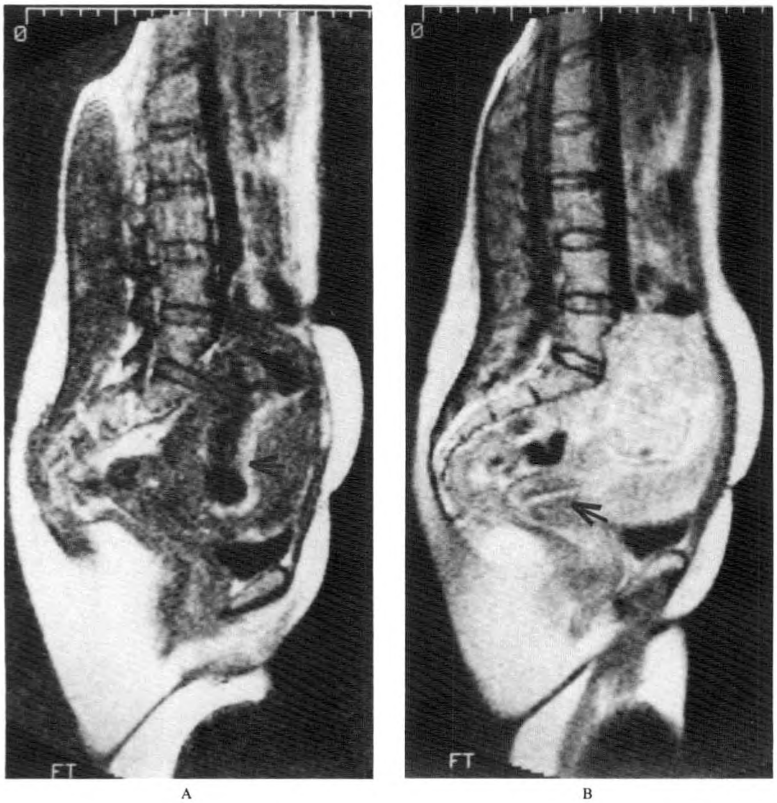

FIG. 3.

(A) Inversion-recovery sequence with TR 2000 ms, TI 600 ms. Paramedian sagittal section through the uterus demonstrating haemorrhage within the hydatidiform mole (arrow). (B) Spin-echo sequence with TR 1000 ms, TE 40 ms. Median sagittal section through the same mole. The trilaminar cervix can be seen (arrow).

80 ms). The molar tissue within the uterus is, again, seen to have a characteristically high signal.

Molar tissue using a spin-echo sequence such as the above gives an image with good anatomical resolution but is not able to distinguish between blood and molar tissue.

In a different patient, Fig. 3 shows the different images that can be obtained using an inversion-recovery sequence which produces a T_1 weighted image. This is able to discriminate haemorrhage within the molar tissue. In Fig. 3A this is seen to give an area of high signal adjacent to the molar tissue, which has a very low signal, implying a long T_1 relaxation time for this type of tissue. Figure 3B shows the same mole but with an image produced by a spin-echo sequence. In Fig. 3B the cervix in this particular case is seen to have a trilaminar appearance. The cervical mucus has a high signal surrounded by two low-intensity bands and, on either side of these, a rim of myometrium. The cause of this appearance has created considerable interest but its origin is uncertain (McCarthy et al, 1985).

DISCUSSION

Magnetic resonance imaging has been shown to be the equal of ultrasound in the detection of molar tissue. Recent reports have now documented the non-specificity of ultrasound in first-trimester molar pregnancies (Woodward et al, 1980) and invasive trophoblastic disease (Fleischer et al, 1978). The variable sonographic appearances of hydropic degeneration of the placenta and its confusion with true hydatidiform mole have been shown (Buschi et al, 1979). Molar tissue has been seen to have a characteristic appearance on MRI in hydatidiform mole. The myometrium is clearly shown as a separate structure and this allows accurate assessment of invasion. The high specificity for trophoblastic disease using MRI leads us to believe that this will be a very useful technique for the early detection of recurrent trophoblastic disease associated with a rising HCG titre. Due to the high signal associated with molar tissue, local metastases in the vagina and pelvis as well as distant disease should be detected.

Ultrasound will probably remain the principal diagnostic technique in the detection of molar tissue; however, magnetic resonance imaging may offer advantages over ultrasound in terms of earlier detection, assessment of invasion and detection of recurrent tumour.

ACKNOWLEDGMENTS

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A method for the clinical measurement of relaxation times in magnetic resonance imaging

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ABSTRACT

A method for the determination of relaxation times in clinical magnetic resonance images is described. Three components are measured: the spin-lattice (T_1) and spin-spin (T_2) relaxation times and the proton density (M_∞). These components are separated in the algorithm to give increased tissue discrimination. Multiple data points are used to minimise error and increase reproducibility. Errors that arise in imaging data because of the short sequence repetition periods are considered and a technique for their reduction described. Clinical results obtained using the method are reviewed. These results demonstrate the clinical utility of the technique.

The purpose of this paper is to describe a method for the measurement of clinical relaxation times in magnetic resonance imaging. With this imaging technique, quantitative tissue characterisation is possible by determination of three signal parameters. The magnetic resonance (MR) signal may be described using the spin-lattice (T_1) and spin-spin (T_2) relaxation times and its maximum value (M_∞). The problem is to separate the three components and ensure their independence. They may then be used to assist in the characterisation of a given tissue.

In clinical imaging a major problem in the measurement of T_1, T_2 and M_∞ is the limited time available. The signal-to-noise ratio is approximately proportional to the scanning time. While *in-vitro* investigations may be conducted with very long repetition periods which effectively separate the relaxation times, this is not normally practicable in clinical imaging. It is often difficult for patients to lie still in the instrument for periods exceeding 1 h. In many instances economic considerations require an efficient use of the machine and a minimum time period for each patient. Moreover, images are generally formed in the presence of a strong slice-select gradient. This, combined with radio-frequency (RF) and magnetic-field inhomogeneity and patient movement, are some of the particular problems involved in quantitative MR imaging.

Here we describe an algorithm for the separation of the MR parameters from imaging data. The technique is supported by both clinical and experimental results which indicate discrimination and reproducibility.

METHODS AND RESULTS

We consider measurement of T_1, T_2 and M_∞ from saturation-recovery (SR) (McDonald & Leigh, 1973; Waterton et al, 1984) and spin-echo (SE) pulse sequences. This algorithm has evolved from the measurement of several thousand relaxation times from clinical and experimental data obtained on a Picker superconducting whole-body imaging system operating at 10.98 MHz. All relaxation processes are taken to be monoexponential and the validity of this assumption is considered. We first consider measurement of T_1 using spin echo and then modify the algorithm for saturation recovery. For small-field, high-resolution studies spin echo is used to determine T_1 but in our clinical studies saturation recovery is more appropriate.

Estimation of T$_1$ *using spin echo*

To measure T_1 using spin echo (90°–τ–180°–τ–[echo]) the scans have a fixed tau with the repetition time, T_r, varied. Contrast in an individual SE image is a function of both T_1 and T_2 relaxation in addition to M_∞. However, T_1 is measured using the variation in signal strength with the repetition period. From the Bloch equations (*e.g.* Abragam, 1961), the relationship between signal strength, S, and the relaxation times is:

$$S = M_\infty Z \, e^{-2\tau/T_2} \tag{1}$$

$$Z = 1 - 2\, e^{-T_r/T_1} e^{\tau/T_1} + e^{-T_r/T_1} \tag{2}$$

where τ is the interval between the 90° and 180° RF pulses and M_∞ the maximum magnetisation along the z axis, which is often described as the proton density.

The first step is to obtain an initial estimate of M_∞. When τ is much smaller than T_r, Equation (1) can be simplified and reduces to:

$$S \simeq \bar{M}_\infty (1 - e^{-T_r/T_1}) \tag{3}$$

where

$$\bar{M}_\infty = M_\infty e^{-2\tau/T_2}$$

As an initial estimate of $\bar{M}_\infty$, which may be considered as a T_2-weighted proton density, an SE scan with a short tau and a long repetition time, T_{r1}, is used. The repetition time is chosen such that it is greater than or equal to three times the longest T_1 normally

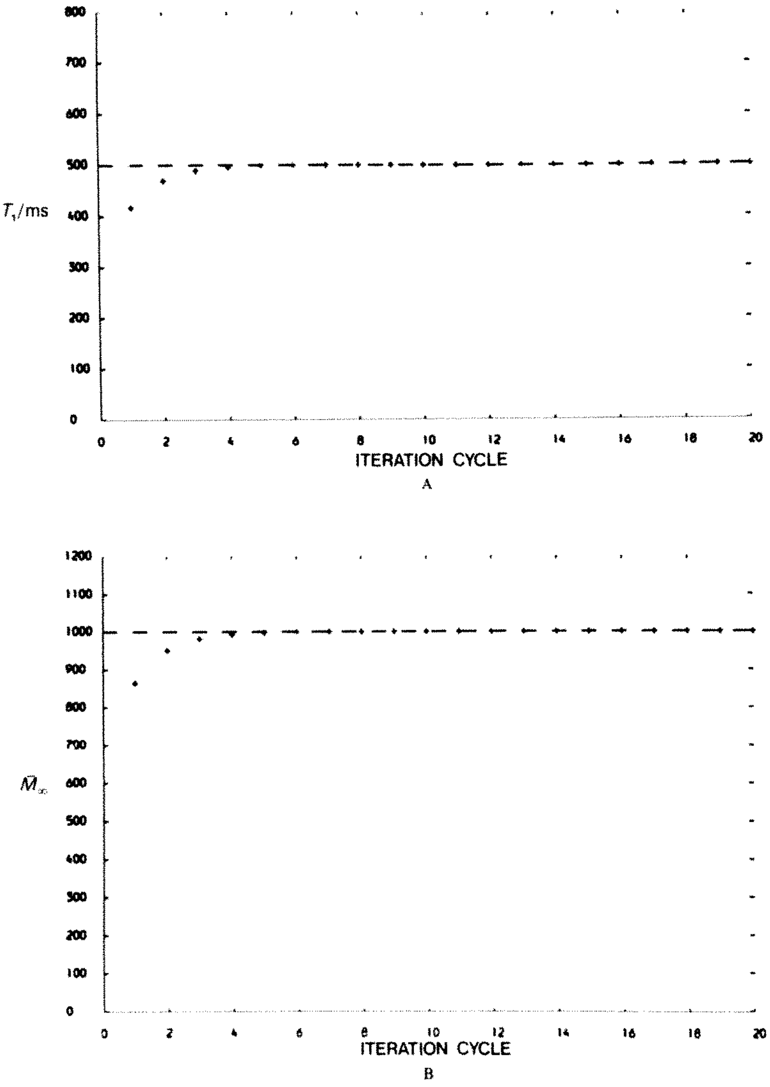


FIG. 1.

The convergence of the first iteration for SE data is illustrated. A similar result is obtained for SR data. This iteration corrects for the relatively short repeat time used for the estimate of $\bar{M}_\infty$. A "long" repetition period of 1000 ms was used in Equation (3) with $T_1 = 500$ ms and $\bar{M}_\infty = 1000$ ms. In (A) the rapid convergence of the T_1 estimate is shown, while (B) gives the corresponding result for $\bar{M}_\infty$ estimates.

encountered in the tissue. Under this condition Equation (3) reduces to:

$$S_l \simeq \bar{M}_\infty \qquad (4)$$

where S_l is the signal from the long T_r scan.

To calculate an initial T_1 estimate, Equation (3) is rearranged in log linear form:

$$\ln(1 - S/\bar{M}_\infty) = -T_r/T_1 \qquad (5)$$

Substituting the S_l value for $\bar{M}_\infty$, a least-squares regression line is calculated (Moore & Edwards, 1965) for data from a series of scans with the repetition time varied. An estimate of T_1 is obtained from the slope of the line.

This initial T_1 estimate, $\bar{T}_{11}$ is used in Equation (3) with S_l to calculate a second value, $\bar{M}_{\infty 2}$, from which a further relaxation time estimate, $\bar{T}_{12}$, is obtained using Equation (5). The iteration is continued for n cycles until

$$\bar{T}_{1n} - \bar{T}_{1(n-1)} < E_1$$

where E_1 is some predetermined error condition. This iteration is efficient and rapidly convergent, as shown theoretically in Fig. 1. In this calculation for a severe test a "long" repetition time of only 1000 ms was used with $T_1 = 500$ ms and $\bar{M}_\infty = 1000$. For clinical data two or three iterations are required with $E_1 = 0.5$ ms.

This first estimate of T_1 has been calculated using the simplified form of Equation (1) and is, therefore, only an approximation. The error in the $\bar{M}_\infty$ estimate is small as the long repetition time is much larger than the tau value. However, the estimates are now refined in a second iteration using the full log linear form of

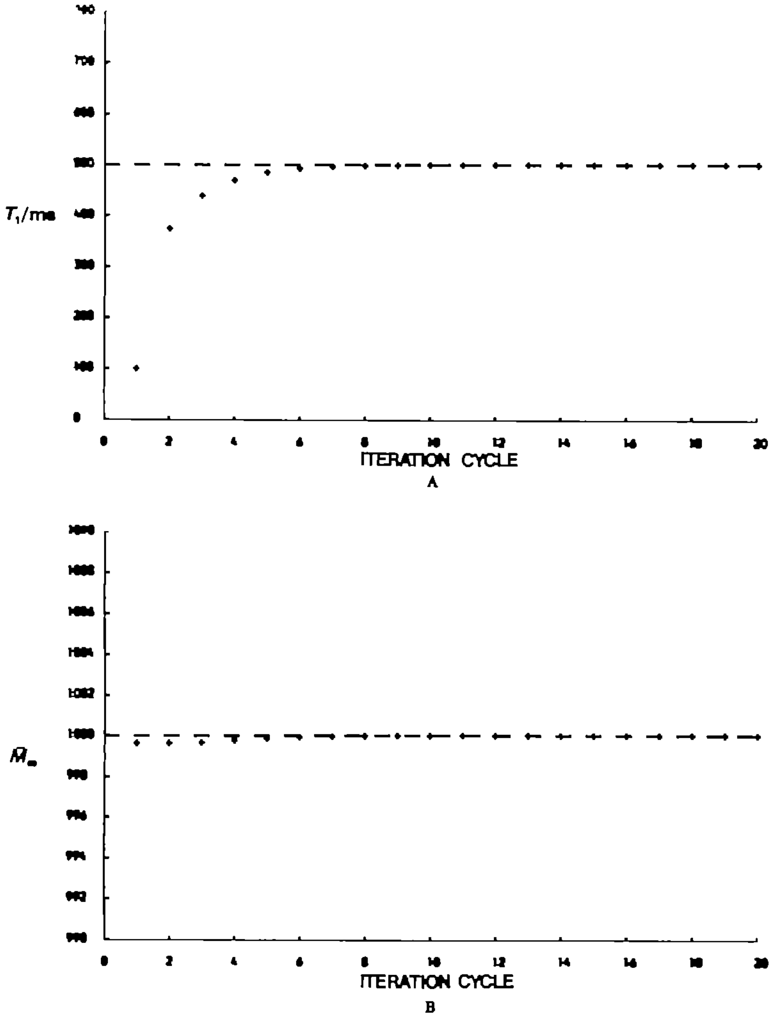


FIG. 2.

Convergence of the second iteration for SE data is shown. The true values are $T_1 = 500$ ms and $\tilde{M}_\infty = 1000$ ms with a 4000 ms repetition period used for the $\tilde{M}_\infty$ estimate. A low initial T_1 estimate of 100 ms was assumed. The estimates of T_1 converge rapidly, as shown in (A). Only a small refinement of the $\tilde{M}_\infty$ estimate is required, as illustrated in (B).

Equation (1):

$$\ln\left(1-\frac{S}{M_\infty}+e^{-T_r/T_1}\right) = -\frac{(T_r-\tau)}{T_1}+\ln(2) \qquad (6)$$

The approximate solutions $\tilde{M}_{\infty s}$ and $\tilde{T}_{1s}$ are substituted into the left hand side of Equation (6) and it is solved using linear regression to give $\tilde{T}_{11}$. The iteration is terminated after m cycles, when a second predetermined error condition, E_2, is achieved for $\tilde{T}_1$. The result is a new estimate of the spin lattice relaxation time, $\tilde{T}_{1m}$, from which a further estimate of the proton density, $\tilde{M}_{\infty m}$, is calculated using

$$\tilde{M}_{\infty m} = \frac{\tilde{M}_{\infty s}(1-e^{-T_r/\tilde{T}_{1m}})}{(1-2\,e^{-T_r/\tilde{T}_{1m}}\,e^{\tau/\tilde{T}_{1m}}+e^{-T_r/\tilde{T}_{1m}})} \qquad (7)$$

This iteration is rapidly convergent. Figure 2 shows the theoretical convergence for $T_1 = 500$ ms with an initial estimated T_1 of only 100 ms and a long repetition time of 4000 ms. In practice, this iteration is a refinement of an initial close estimate and only two or three cycles are required with $E_2 = 0.05$ ms.

Estimation of T$_1$ *using saturation recovery*

The algorithm employed for T_1 calculation from saturation-recovery data is similar to that used for spin echo. Standard saturation-recovery sequences have slice profiles that vary with the repeat time and are generally not suitable for measurement of T_1 in imaging (*e.g.* Bryant et al, 1984). The sequence we use is fully described elsewhere (McDonald & Leigh, 1973; Waterton et al, 1984) but contains two 90° pulses separated by an interval much greater than T_2^* and a similar interval follows the second pulse. The effective repeat time, T_r, follows the second 90° pulse and a spin-echo data collect is used with fixed τ. The true repeat time is, thus, greater than T_r. In this way, T_2^* decay is used with the two 90° pulses to remove the "memory" of the previous pulse train, making the sequence

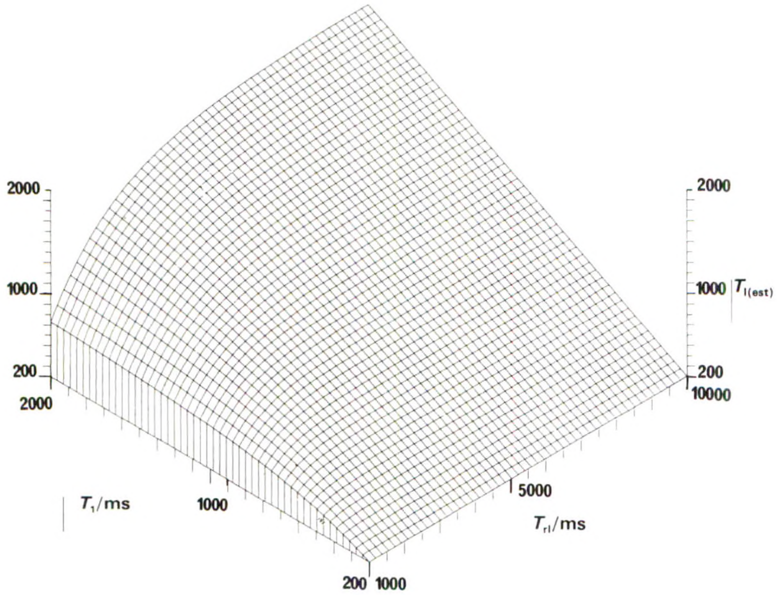


FIG. 3.

The relationship between the T_1 value and its estimate $T_{1(\mathrm{est})}$ is shown here for a range of values of the long repetition period T_{r1}. Large errors in the measured T_1 value may result from the use of relatively short values of T_{r1}.

relatively insensitive to both RF inhomogeneity and variation in the slice profile with T_r. The equation for the signal, S, in saturation recovery is:

$$S = M_\infty \, \mathrm{e}^{-2\tau/T_2}(1-\mathrm{e}^{-T_r/T_1}) \qquad (8a)$$

This equation is of the same form as the approximation in Equation (3) used in the initial spin-echo calculation. However, it is now an exact expression and, therefore, the second iteration is no longer required. The spin-echo data collection results in the long repeat time M_∞ estimate being T_2-dependent, as with the SE sequence.

Effect of the $\bar{M}_\infty$ *estimate on* T_1

If uncorrected, the short repetition periods used in imaging can reduce tissue discrimination. The relatively short repeat time used to estimate $\bar{M}_\infty$ results in underestimation of T_1. The iterations effectively correct for this and extend the range of calculated T_1 values. If no correction is made, the potential for discrimination is reduced. The effect of the long repeat time correction is shown here both theoretically and experimentally. Equation (8a) may be rewritten:

$$S = \bar{M}_\infty(1-\mathrm{e}^{-T_r/T_1}) \qquad (8b)$$

which gives, using Equation (4):

$$T_1 = -T_r/\ln(1-S/S_1) \qquad (9a)$$

Substituting the expressions for S (Equation (8a)) and S_1 (Equation (8a) with a long repeat time T_{r1}) gives an uncorrected T_1 estimate of:

$$T_{1(\mathrm{est})} = T_r/\ln\left[(\mathrm{e}^{-T_r/T_1}-\mathrm{e}^{-T_{r1}/T_1})/(1-\mathrm{e}^{-T_{r1}/T_1})\right] \qquad (9b)$$

The form of this equation is shown graphically in Fig. 3. This figure indicates the magnitude of the error corrected in the algorithm. In this calculation a T_r value of 20 ms was assumed. The errors in the estimated T_1 in Fig. 3 are reduced by the correction for $\bar{M}_\infty$ in our algorithm.

Our experimental results are consistent with the theoretical predictions. Experimental results were obtained using 34 glass tubes (2.6 cm diameter) filled with different concentrations of copper sulphate solution in double-distilled water. An ideal substance for calibrating imaging systems is not available. We used copper sulphate ($T_1 \simeq T_2$) for our experiments as

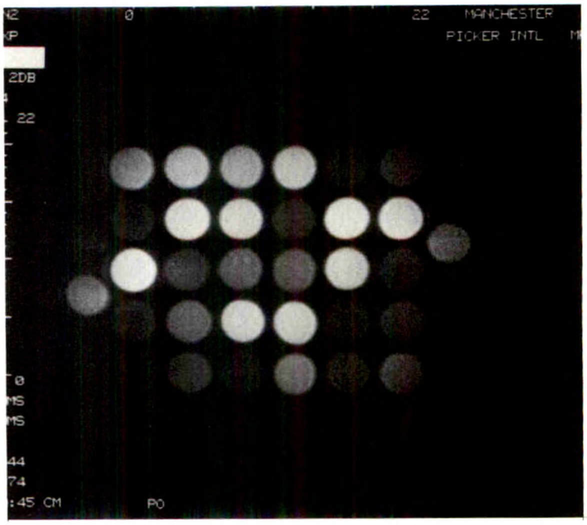


FIG. 4.

An SR image of an array of 34 glass tubes. Each tube contained a different concentration of copper sulphate solution placed in a random order within the array.

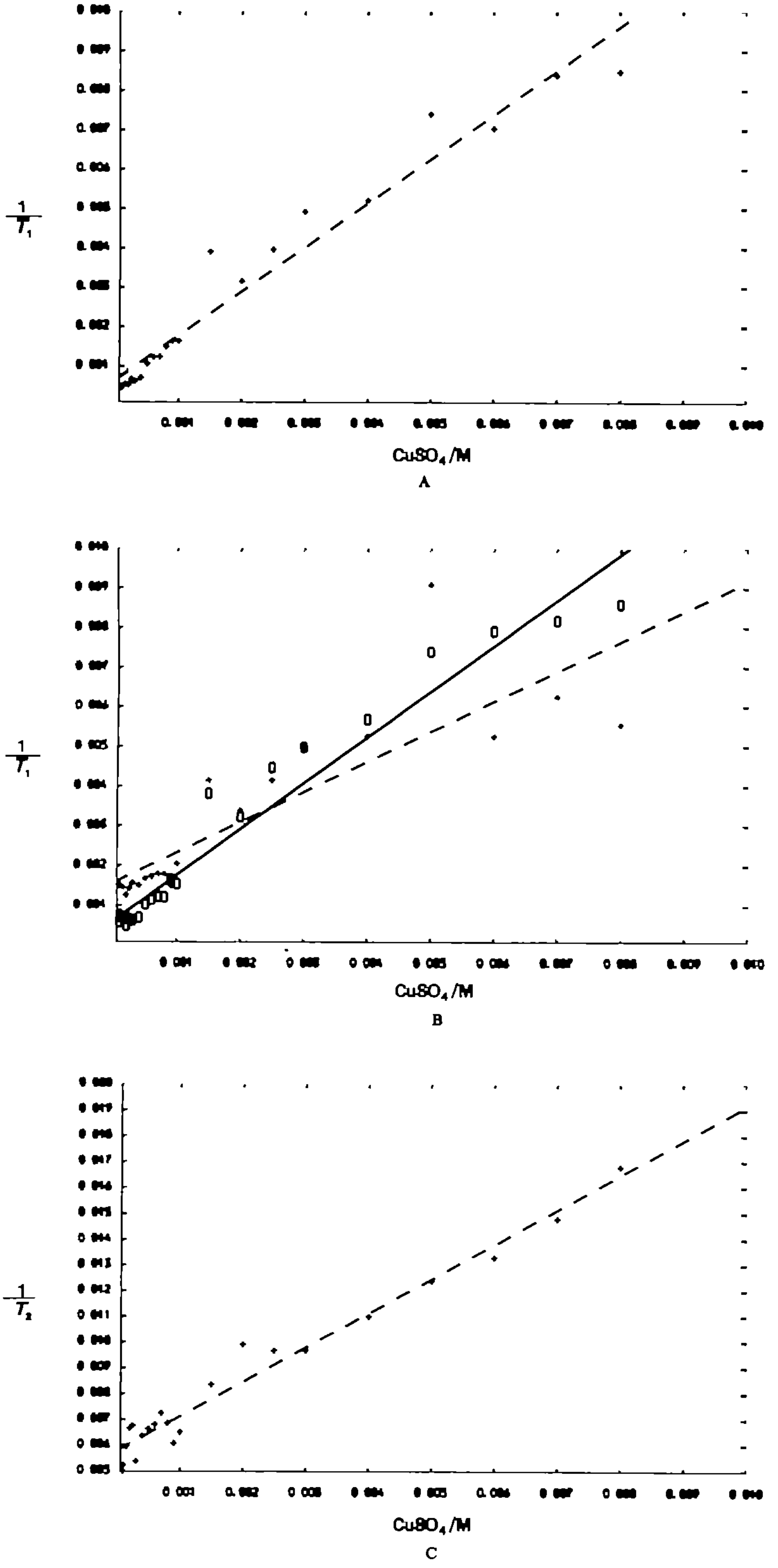


FIG. 5

(A) Corrected SR T_1 estimates for the copper sulphate solutions in the phantom shown in Fig. 4. The long repetition period was 4000 ms. A least-squares regression line fit to the data is indicated by the broken line. (B) The effect of the iterated $\tilde{M}_\infty$ correction. Initial (+) and corrected (O) data obtained using a "long" repetition time of 1500 ms. Results from the corrected values are similar to those obtained with the 4000 ms $\tilde{M}_\infty$ estimate in (A), as shown by comparing the regression lines. Corresponding T_2 results are shown in (C). Further details are given in the text.

the ratio of T_1 to T_2 was not important in validating the algorithm. These tubes were placed in a random order in an array within the imaging field. A saturation-recovery image of this phantom is given in Fig. 4. The phantom was scanned using 17 different saturation-recovery T_r values ranging from 50 ms to 4000 ms. Each scan was repeated 10 times. The temperature of the phantom was 20°C throughout the experiment. Mean pixel value standard errors were within 1%. In the absence of an ideal test substance, results from human volunteers and our clinical studies were used to indicate the long-term reproducibility and utility of the method.

In Fig. 5A typical saturation-recovery T_1 estimates for the copper sulphate solutions are given. These measurements were made with corrected estimates of M_∞ obtained using a repetition time of 4000 ms. The results, which include errors due to variation with spatial position arising from RF inhomogeneity, have been obtained from a method used in clinical practice. They are not necessarily the most reliable that can be obtained from this particular instrument. When compared with results from a prototype spectrometer (Tingle, 1984) good correlation was obtained ($r = 0.93$, $p < 0.001$). The effect of the iterated correction is shown in Fig. 5B with a repetition time of 1500 ms for estimation of $\bar{M}_\infty$. The dashed line and the solid line are the results of a least-squares fit to the uncorrected and corrected data, respectively. The corrected regression line has the greater slope and gives similar results to those obtained with the 4000 ms $\bar{M}_\infty$ estimates in Fig. 5A.

Estimation of T_2 *and unweighted* M_∞

Here we describe the estimation of T_2 and extraction of the final M_∞ value. The data are normally collected using a series of single-echo, spin-echo sequences with a fixed repeat time and tau values incremented. If a Carr–Purcell sequence (*e.g.* Farrar & Becker, 1971) is used the form of Equation (2) varies with the number of 180° pulses applied and a small modification to the algorithm is, thus, required.

When using data from single-echo sequences with fixed repeat time, Equation (1) is rearranged in log linear form:

$$2\tau/T_2 = -\ln(S/M_\infty Z) \qquad (10)$$

An initial T_2 estimate is obtained by substituting both $\bar{T}_{1m}$ and $\bar{M}_{\infty m}$ estimates into Equation (10) and fitting a least-squares regression line to the SE data. The T_2 and $\bar{M}_{\infty m}$ estimates are then substituted into Equation (3) to obtain an initial unweighted M_∞ estimate. The implied iteration is efficient and continues until a specified minimum error condition, E_3 on T_2, is achieved. Using clinical data, only two or three iterations are normally necessary. Typical results obtained with the phantom containing the array of tubes of copper sulphate solution are given in Fig. 5c. These results again include any variation arising from spatial variation in the images and correspond to values from a clinical method. Comparison with the spectrometer showed good correlation ($r = 0.94$, $p < 0.001$). The phantom was scanned using seven spin-echo tau values ranging from 20 ms to 80 ms. Each measurement was repeated 10 times.

The T_2 values measured on our machine using SE are generally lower than the corresponding T_1 values measured in copper sulphate. Spectroscopic measurements have shown the T_1 and T_2 values of $CuSO_4$ solutions to be similar. We are, thus, underestimating the T_2 values and reducing T_2 and M_∞ discrimination. Similar results found in other imaging studies have been explained in terms of diffusion (Bakker et al, 1984; Wesbey et al, 1984). Carr–Purcell sequences may largely overcome diffusion effects (Farrar & Becker, 1971), but were not available for our initial studies.

Dependence of T_2 *on* T_r

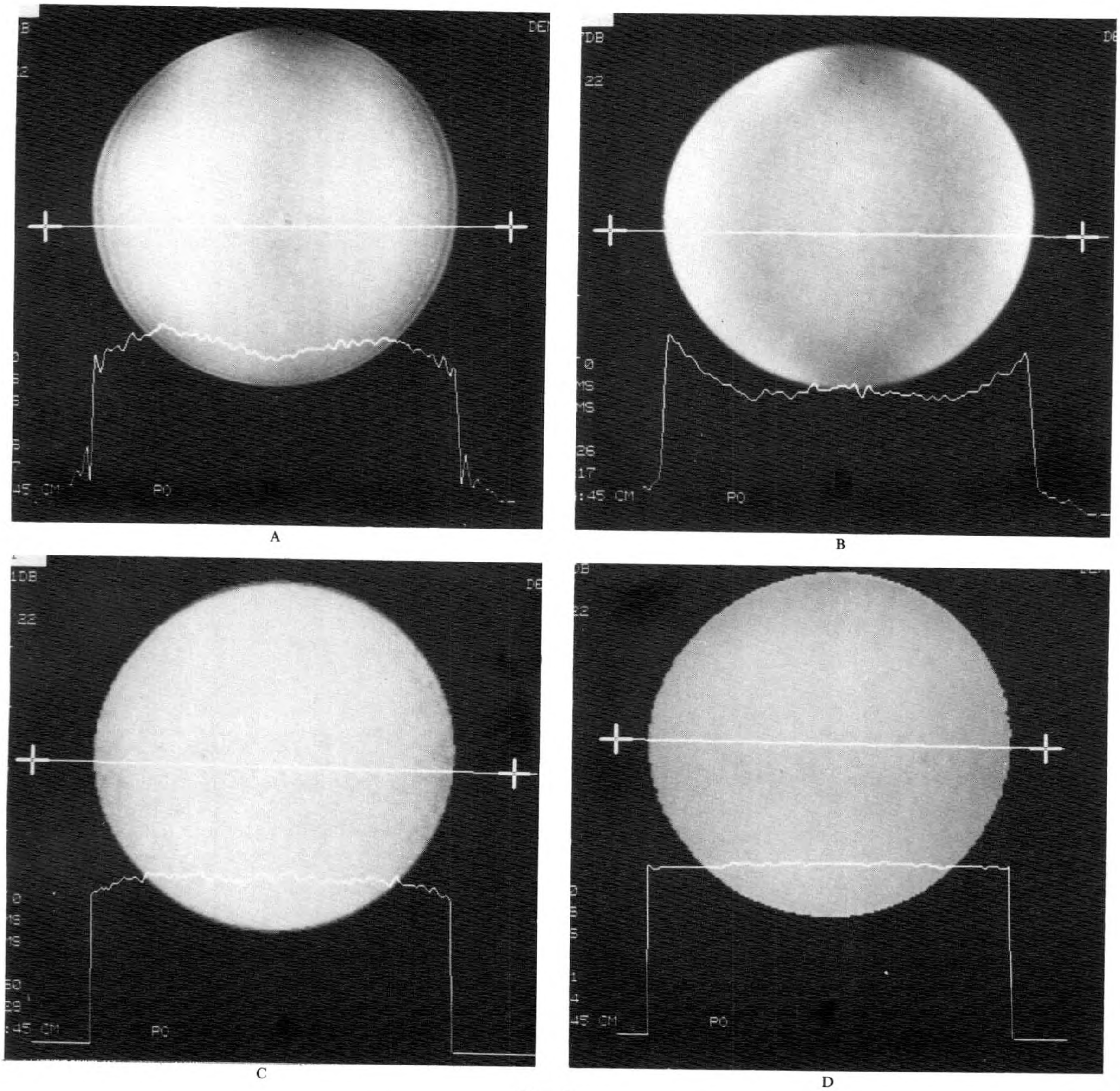
The nature of the spin-echo and Carr–Purcell sequences means that the estimated T_2 has a dependence upon the repeat time. For simplicity we consider the spin-echo equation. The result, however, is valid for and may be extended to the Carr–Purcell sequence. Let Ω be the slope of the logarithmic straight line joining two points defined by tau values τ_1 and τ_2, then from Equation (10) after substitution and some manipulation:

$$\Omega = -\frac{2}{T_2} + \frac{\ln(Z_2/Z_1)}{(\tau_2-\tau_1)} \qquad (11)$$

The second term in Equation (11) is an error introduced into the estimation of T_2 which is dependent upon the repetition period. It should be noted that the ratio Z_2/Z_1 depends upon the tau values of the echoes chosen for measurement.

Choice of sequence

The condition necessary for relaxation measurement is simply that the pixel values are related by the appropriate exponential function. This condition may be met even in the presence of spatially dependent grey-level artefacts in the source images that can arise from RF inhomogeneity. In clinical imaging several pulse sequences have been used to measure relaxation times. However, each sequence may have different image artefacts. When sequences with different artefacts are used together for measurement of relaxation times, spatially dependent errors are obtained in the calculated values. When a single sequence such as saturation recovery is used, the similarity in the artefacts can lead to cancellation in computed relaxation time images. This is illustrated in Fig. 6 where profiles across SR and SE images are shown with corresponding image profiles from seven-point calculated T_1 and T_2 images. We have found limited spatial dependence in our calculated relaxation times, indicating that acceptable quantitative clinical images can be obtained.



A

B

C

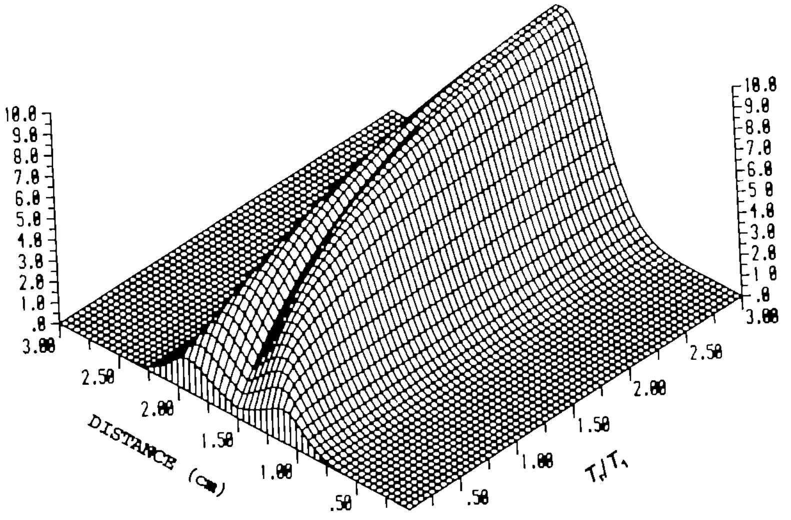
D

FIG. 6.

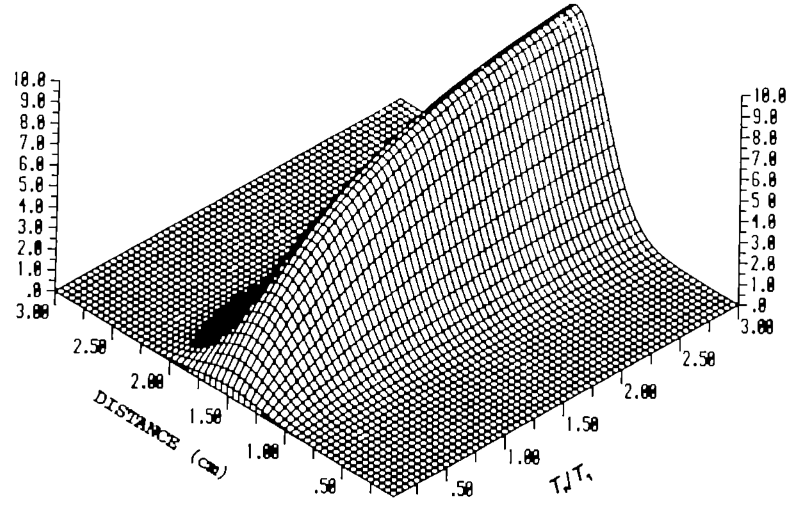
Saturation-recovery (A) and SE (B) images of a 30 cm-diameter blank $CuSO_4$ phantom are shown. Profiles across these illustrate the differing artefacts produced by these sequences. These artefacts cancel in the calculated T_1 and T_2 images of the same phantom as shown by images (C) and (D), respectively.

Relaxation-time measurement is not necessarily independent of the slice profile. Perfectly rectangular slice profiles have not been produced and out-of-slice tissue may contribute to the signal. The effect of such out-of-slice artefacts on T_1 and T_2 calculations can be small and may often be ignored (Robinson et al, 1986). The main effect is a sequence-dependent variation in the profile with repeat time. It is possible, however, to design pulse sequences, as in our saturation sequence, where the profile is relatively independent of the repetition period (Robinson et al, 1986).

Measurements of the slice profile using both direct imaging of a thin slice of material passing through the slice and a field-echo technique (Bryant et al, 1984) indicate little or no variation with our saturation-recovery sequence but a slight broadening with small values of T_r/T_1 for spin echo. Computer simulations of the magnitude profile are shown in Fig. 7 for a standard



F I D sequence
A



S R sequence
B

FIG. 7.

Computer simulations of the magnitude slice profile (Gaussian) in (A) a simple FID and (B) our saturation-recovery sequence. With low values of T_r/T_1 the profile of the FID becomes bimodal while the SR sequence retains the Gaussian form.

free induction decay (FID) (90°–τ–90°) and our saturation-recovery sequence. This simulation assumes a Gaussian slice profile which is iterated recursively with the RF pulses simulated by simple rotation matrices. As can be seen, the FID profile varies considerably with T_r/T_1, while only the amplitude of the saturation-recovery profile varies; its shape remains constant.

Angular discrimination error

Errors in the estimated relaxation times vary with the value to be measured. Following logarithmic transformation both T_1 and T_2 values are angular measures of their regression lines. Consider the T_2 value:

$$T_2 = -2/\tan\phi \qquad (12)$$

where tan ϕ is the slope of the regression line. We may define ϕ with reference to the range of the tau periods used in the estimation

$$\phi = (\bar{S}_2-\bar{S}_1)/(\tau_2-\tau_1) \qquad (13)$$

where τ_2 and τ_1 are maximum and minimum tau values, respectively, and the corresponding least-squares estimates of the transformed signal values are S_2 and S_1.

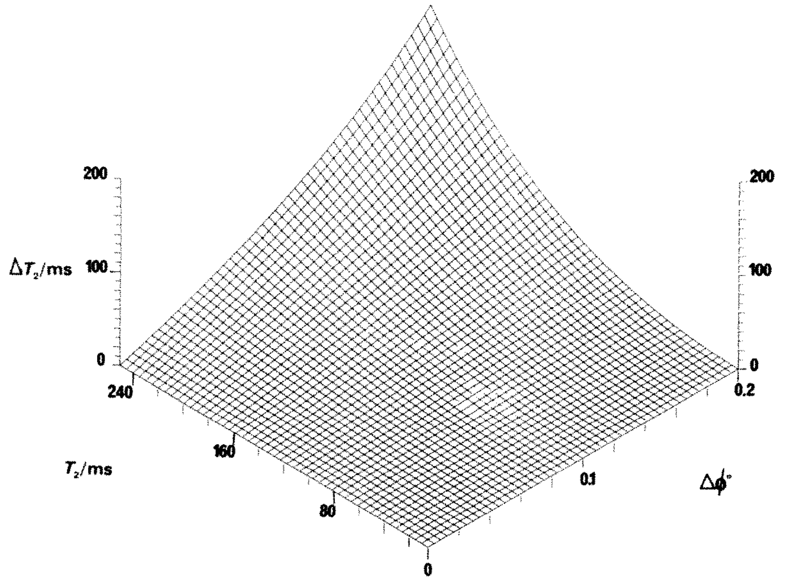


FIG. 8.

The effect of the angular discrimination error on T_2 estimates is indicated. For a range of angular errors on the least-squares regression line from 0° to 0.2°, the relationship between the true T_2 and the error in the estimated value, ΔT_2, is shown.

For an error ΔT_2 that corresponds to an angular error, ϕ, then:

$$\Delta T_2 = 2\,(\cot\,(\phi+\Delta\phi)-\cot\,\phi) \qquad (14)$$

For long T_2 values, as $\phi \to 0$, a small error in the slope of the regression line results in large ΔT_2 values. Figure 8 illustrates the relationship between ΔT_2, T_2 and $\Delta\phi$. The value of $\Delta\phi$ was assumed to vary between 0° and 0.2°. A similar surface is predicted for T_1. If discrimination is required between long relaxation times then a small error in the estimate of the slope is necessary. This may be achieved by choice of a large range (τ_1 to τ_2) of tau values and a sufficient number of data points.

If T_1 and T_2 are small, using large values of T_r and τ leads to errors in estimating T_1 and T_2. For T_1 measurement, from Equation (9a), S must be less than S_1. If $T_r \simeq 5T_1$, $S \simeq 0.995S_1$ and noise can then make $S > S_1$, so causing the algorithm to fail. When estimating T_2, at large values of τ, S is small and as errors on S can only be positive at these values of τ, this leads to an apparent lengthening of T_2. One method of overcoming these difficulties is not to use T_r or tau values greater than some proportion of T_1 or T_2. With a short-term pixel value reproducibility within 1% we chose a 5% error limit. Thus, for measurement of T_1:

$$T_r < 2.995T_1$$

and for T_2:

$$\tau < 1.498T_2$$

with T_r as large as is practicable. Imaging sequences generally have minimum values for both τ and T_r. Such limits are machine-dependent or a function of the sequence itself. Given limited imaging time, the range of time intervals for study of a particular tissue needs to be considered carefully and pilot experiments are indicated for optimal choice. Relaxation curves for human muscle are shown in Fig. 9. These curves illustrate typical results for living tissue. In Fig. 9A corrected (T_1 = 511 ms, r = 0.998) and uncorrected (T_1 = 543 ms, r = 0.994) data curves for saturation recovery are shown by the full and broken lines, respectively. The corresponding spin-echo decay curve (T_2 = 51 ms, r = 0.989) is shown in Fig. 9B.

Multiexponential decays

An assumption in our approach is that the T_1 decay is monoexponential. For an estimate made on a large area of homogeneous tissue this appears to be a reasonable approximation. If an area contains more than one tissue, such as muscle and fat, a multiexponential decay might be expected. However, it is established that a single exponential closely represents the variation of a multiexponential decay unless the separate components differ by a factor greater than three (Koenig et al, 1984). Since our multipoint method gives correlation coefficients typically greater than 0.99, it may not be possible to obtain sufficient data points to measure multiexponential T_1 decays in clinical imaging. This is illustrated in Fig. 10. Values of the coefficient of determination, r^2, are shown in Fig. 10 for a single T_1 fit to a two-component decay. The coefficient of determination is the square of the correlation coefficient and may be considered as the explained variation divided by the total variation (Moore & Edwards, 1965). Ten equally spaced signal measurements at tau values up to 1000 ms were assumed with one T_1 component fixed at 500 ms. The value of r^2 is shown for a large range of values of the second spin-lattice decay T_1 and $M_{\infty 1}/M_{\infty 2}$. Almost all the variation

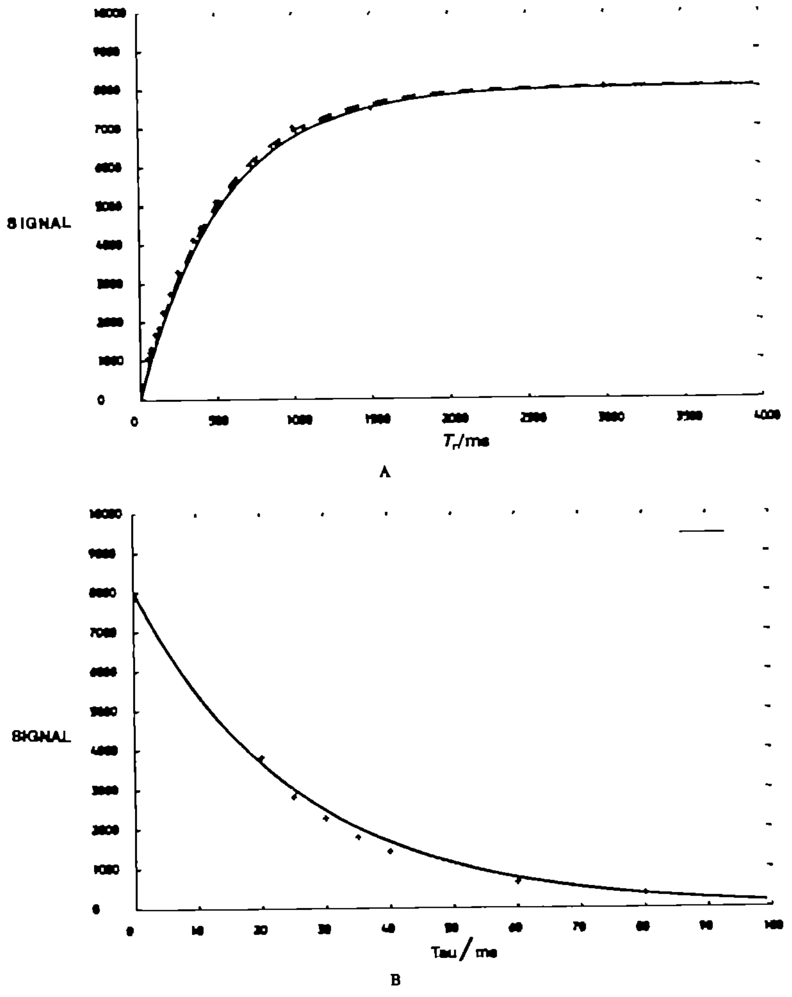


Fig. 9.

Typical results from human leg muscle obtained using SR and SE sequences. In (A) the relaxation data for the SR sequence are shown. An uncorrected least-squares fit is indicated by the solid line with an estimated T_1 of 543 ms ($r = 0.994$) and the corrected fit by the broken line with T_1 equal to 511 ms ($r = 0.998$). The corresponding SE relaxation is shown in (B) with T_2 estimated to be 51 ms ($r = 0.989$).

is explained by a single parameter fit, even when the difference between the relaxation times is large.

With T_2 relaxation times there is some evidence for multiexponential decay (Gersonde et al, 1984). Using Carr–Purcell sequences, sufficient data points may be obtained to calculate multicomponent decays on some imaging machines. However, great care is needed in the interpretation of multiexponential data. It is necessary to show that the components are not sequence or instrument artefacts. Reproducibility must be demonstrated and it is necessary to show statistically that the multiple components explain more of the variation in the data with the reduced number of degrees of freedom. Only when this is done should their possible physiological importance be considered. It is possible that multicomponent T_2 parameters could give a greater clinical characterisation of some tissues, but this has yet to be demonstrated. A single-component T_2 decay obtained reproducibly is clinically useful, as our results show.

Clinical results

Here we present preliminary results on the discrimination of T_1 and T_2 values in our clinical studies. There was little difference in results obtained from phantom studies 1 year apart. However, these results may not be directly applicable to patients where other factors such as coil loading and movement are important. We have, therefore, used results from *in-vitro* human studies to demonstrate both stability and clinical utility. As a typical example, consider our results from degenerate nucleus pulposus over a 2-year period ($T_1 = 420.9 \pm 27.8$ ms, $T_2 = 51.1 \pm 2.2$ ms) where both machine and biological variations are included. In this study the T_1 and T_2 values were measured in normal and surgically proven degenerate intervertebral discs. Full details of the clinical method are given elsewhere (Jenkins et al, 1985a). Both the T_1 and T_2 values of the normal disc decreased with age over a range of 8 years to 75 years. However, there was no significant correlation between proton density and age. When

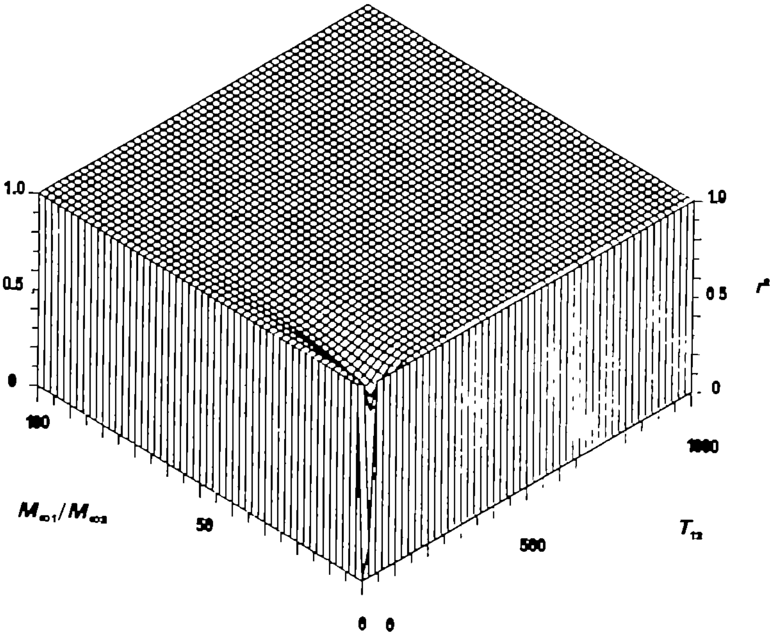


FIG. 10

The coefficient of determination (r^2) is shown for the fit of a single exponential to a two-exponential decay. The first decay is described by $M_{\infty1}$ and T_{11} which is fixed at 500 ms. The second decay is described by $M_{\infty2}$ and T_{12} The plateau of the coefficient of determination is close to unity over the clinical range

grouped into decades, an analysis of variance for unpaired samples (Moore & Edwards, 1965) showed at a highly significant confidence limit ($p < 0.01$) that the T_1 groups were not sampled from the same normal populations. Similar results (at $p < 0.01$) were obtained from an analysis of variance from the T_2 groups. The corresponding results for proton density (M_∞) were not significant ($p > 0.05$). A series of Student's *t*-tests comparing the normal T_1 groups with the degenerate discs demonstrated a highly significant difference ($p < 0.01$) at all ages. Similarly, the differences between the mean T_2 values of the normal and degenerate discs were highly significant ($p < 0.01$) except for the sixth decade which was significant ($p < 0.05$) and the seventh decade in which there was no difference ($p > 0.05$).

Highly significant ($p < 0.01$) discrimination has also been demonstrated in our clinical studies for T_2 values between benign prostatic hypertrophy and prostatic tumour (Jenkins et al, 1985b). Similar results (at $p < 0.01$) for T_1 have been obtained for discrimination between chronic pancreatitis and normal pancreas (Jenkins et al, 1985c) and between medial frontal white matter in patients with dementia and age-matched controls.

DISCUSSION

A robust method for the estimation of T_1, T_2 and M_∞ from clinical images has been described. The effect of relatively short repeat times is accounted for to a first approximation. This technique allows separation of the independent parameters. In imaging it is necessary to estimate T_1, T_2 and M_∞ together because of the short repeat times. Some variability in the measurement of M_∞ over a long time period appears to be machine-dependent. Use of a calibration phantom would be expected to reduce this variation. Over a 2-year period the relaxation time measurements in patients have been highly reproducible, enabling good tissue discrimination to be achieved. Spin-lattice relaxation times are often monoexponential in clinical imaging. Determination of a single T_1 is sufficient unless there is a physiological or other reason for considering the possibility of large differences in T_1 with multiexponential relaxation times. A statistical test of the relative goodness of fit of the two methods can be applied, provided sufficient data points have been obtained.

It has been suggested that MR parameters might be generally useful for tissue characterisation (*e.g.* Mansfield & Morris, 1982). Indeed, the production of image contrast depends upon variation in T_1, T_2 and M_∞ values in the signal from the body. In an ideal case, a single parameter, say T_1, would uniquely characterise a tissue and its pathology, as in our results for the intervertebral disc. However, it is clear that such discrimination will, in general, be on the basis of probability, because of biological and other variation. Obtaining all three parameters increases the probability of tissue characterisation. Further parameters which, alone, have a low probability of characterisation could improve the predictive capacity of MR, such as multiple T_2 components, relative frequency distributions of T_1, T_2 and M_∞ of pixels in the area of interest or image texture parameters (Haralick, 1979; Connors & Harlow, 1980).

We have shown that it is possible to obtain robust and reproducible clinical tissue discrimination by measurement of relaxation times on a clinical imaging system. However, there is at present no reason to suppose that any two instruments would give the same value, even at the same field strength. At present there are no national or international standards for relaxation time measurement. Values quoted in the clinical literature are, therefore, at best, only internally consistent and reproducible. Quoted values vary with the imaging instrument, field strength and pulse sequence used. If MR relaxation times are to be of general clinical utility, standards are needed.

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Fast computer processing for tissue highlighting in computed tomographic cross-sectional imaging and digital scan projection radiography

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ABSTRACT

A simple, fast, computer method of simultaneously highlighting edge detail and emphasising soft-tissue contrast is discussed. An objective comparison is made with conventional blurred mask subtraction using the signal-to-noise ratio from phantom scans. The use of the algorithm for inner ear studies and digital scanned projection radiography is presented.

Computed tomography images can be considered to be composed of three distinct regions: one of low-density air, one of approximately unit-density soft tissue and one of high-density bony tissue. Conventional display facilities not only allow all of these regions to be viewed but also allow each to be seen individually by windowing. However, problems are encountered when viewing the boundaries between widely separated density regions. Here the dynamic range of pixel values is high, necessitating a wide window, yet the relevant diagnostic information may well be present as small density changes, requiring a small window. This is an established problem in more general imaging applications (Gonzalez & Wintz, 1981) and has been restated more recently for digital scanned projection radiography (DSPR), by Kalender et al (1983). Clinical work by Bentson et al (1980), Hanafee et al (1980) and Shaffer et al (1980) identifies the inner ear as an area where these problems hinder diagnosis. Within our own Institute similar problems were highlighted by the emergence of examinations requiring gas cisternography for investigations of acoustic neuroma.

In addition to hardware viewing aids there are "software" techniques for edge detail enhancement, most of which are based upon blurred mask subtraction. These are summarised in a medical context by Jackson and Kaye (1982), although, in common with many authors, examples are quoted primarily from research studies on digitised chest radiographs. With existing techniques the twin aims of preserving tissue contrast, as an aid to characterisation, and highlighting edge detail, can conflict or lead to complex solutions that impose heavy computational penalties (Cocklin et al, 1982). At the Christie Hospital, line-by-line histogram specification and homomorphic Fourier filtering enhancement have been investigated (Moore, 1982). However, while effective, these methods are inherently complicated and too time consuming for true interactive clinical use.

The following description deals mainly with a comparison of blurred mask subtraction and a suggested alternative approach that is faster, simpler and more easily understood by clinicians.

THEORETICAL BACKGROUND

Blurred mask subtraction

All the blurred mask subtraction techniques can be described as modifications to an established technique. Given a medical image, M, and a blurred version of the same, M_b, a new image, M_s, that enhances the edge detail of the original image can be generated by subtraction. The enhanced image can, in turn, be multiplied by a factor W, to emphasise the edge detail produced by the subtraction and the result added to the original, M, to preserve soft-tissue contrast. If the final, processed image is M_p then the procedure can be written as:

$$\text{subtraction} \quad M_s = M - M_b \qquad (1)$$

$$\text{enhancement} \quad M_p = M + WM_s \qquad (2)$$

More sophisticated methods, such as statistical differencing and weighted unsharp masking, do not attempt to modify the rationale of blurred subtraction but, instead, try to control the inherent problems of over-enhancing strong edge features and emphasised noise. The computational expense of these techniques prohibits general use.

There are obstacles within the blurred mask subtraction technique. The very process of blurring the parent image, M, to produce M_b, leads to a reduction of signal amplitude upon later subtraction. The total edge signal available in the original image is difficult to preserve in this manner.

Figure 1 depicts the subtraction of a one-dimensional top hat signal, T, and its blurred equivalent, T_b. T_s is the result of subtraction which is smeared spatially to a degree dependent on the spatial extent of blurring used to produce T_b.

To preserve contrast the blurred signal must remain

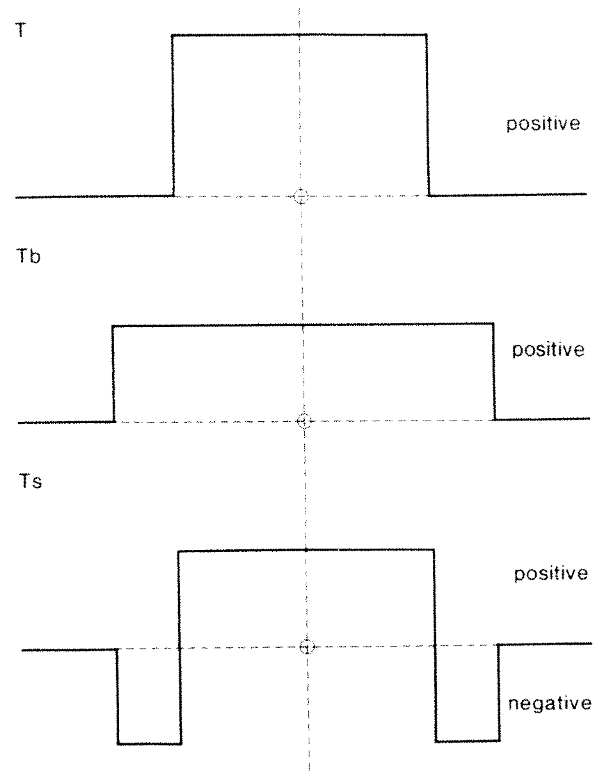

Fig. 1.

Simple edge emphasis by blurring signal T to form T_b, then subtracting to form T_s.

small enough to result in sufficient signal strength upon subtraction to T_s. Otherwise, the emphasis of edge detail will lead to a corresponding loss of contrast.

The subtraction process produces emphasised ringing artefacts because of the positive and negative signal values. Any noise component, whilst being reduced in the blurred image T_b, will be increased upon subtraction. Thus the contrast is reduced and the noise increased by this process leading to a large reduction in the signal-to-noise ratio which can be used as a measure of visual appreciation.

An alternative approach

An alternative approach is to look at the differences in the original image, M, itself. Once again, a variety of methods is available, such as the Roberts' operators or the maximum difference operator (Hall, 1979), which were developed for range compression but were subsequently found to be useful in image enhancement.

A very simple technique is proposed which makes use of the absolute differences in an image, M. Let an image composed of such absolute differences be M_{od}. Once again, a weighting function, W_1 can be defined to boost independently the contribution of M_{od} upon addition to the original image, M. The operation leading to a processed image, M_p, can then be written as:

$$M_p = M + W_1 M_{od} \tag{3}$$

As an extension, we can include a second weight, W_2, to operate on M in Equation (3). This provides an independent and unambiguous way of preserving any desired degree of contrast. The operation to produce a processed image now becomes one in which the two weights act separately to provide control over both contrast and sharpness:

$$\underset{\text{processed}}{M_p} = \underset{\text{contrast}}{W_2 M} + \underset{\text{sharpness}}{W_1 M_{od}} \tag{4}$$

While the same percentage contrast variations can be obtained by the use of weight W_1 alone, in practice this can give image values outside the dynamic range of the visual display monitor and lead to the kind of confusion encountered when deciding on exactly how and which weights to alter in a spatial filter kernel to preserve a required degree of contrast, as well as edge-enhance desirable features. Such filters are often too flexible and difficult to optimise for diverse clinical purposes.

The regions used to generate M_{od} were restricted to the 4 pixels in a 2×2 square. This contrasts with the large range of numerical-filter kernel sizes available on CT scanners. Differences in the horizontal, vertical and, optionally, diagonal directions are summed after conversion to absolute values. Interestingly, the diagonal difference consistently yielded the largest value.

Given an original pixel value $P(x,y)$ at position (x,y), then the transformation to new pixel value $P_1(x,y)$ is given as follows, where ABS indicates the evaluation of the absolute value.

$$\begin{aligned} \text{SUM} = {} & \text{ABS}\,[P(x,y) - P(x+1,y)] \\ & + \text{ABS}\,[P(x,y) - P(x+1,y+1)]^{*} \ \text{differencing and summation} \\ & + \text{ABS}\,[P(x,y) - P(x,y+1)] \end{aligned} \tag{5}$$

*Optional diagonal difference.

$$\underset{\text{processed}}{P_1(x,y)} = \underset{\text{contrast}}{W_2 P(x,y)} + \underset{\text{sharpness}}{W_1 \text{SUM}} \tag{6}$$

This approach is faster than current filtering methods due to the reduced number of operations and can be implemented to provide almost real-time results on scanner-based array processors. In addition, the parameters controlling its implementation are few in number and can easily be understood by clinicians.

Edge Detail and Image Quality

The simple technique described here must provide enhanced images with a quality at least as good as those produced by methods of comparable complexity and intended for replacement. Remarkably, little work has been performed on the assessment of enhanced image quality. Hence, an estimate of the signal-to-noise ratios provided by the suggested alternative and one approach

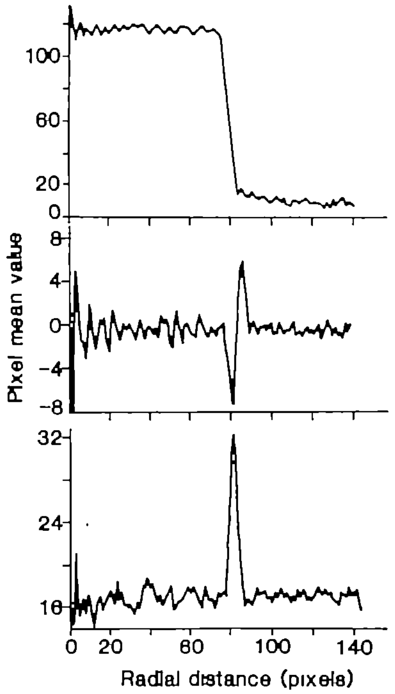

FIG. 2.

The mean pixel value from an annulus plotted against radial distance for a scan of a perspex cylinder in a water-equivalent phantom. Upper: across the perspex-to-water equivalent interface. Middle: interface after subtraction masking. Lower: interface after suggested processing.

TABLE I

EXPERIMENTALLY DETERMINED SIGNAL-TO-NOISE RATIOS

Unsharp mask processing		Difference processing
Upper peak	Lower peak	
0.78±0.087	0.68±0.077	1.67±0.19

to unsharp masking was made from scans of a water-equivalent phantom.

A cylindrical, water-equivalent phantom of 320 mm diameter, with a cylindrical perspex insert, was scanned using an EMI 7070 whole-body machine. This provided images with simulated, low-contrast, water–soft-tissue interfaces. The parent scan was then processed using a CT spatial filter to provide a blurred image suitable for subtraction from the unmodified original. The effects of other numerical filter kernels were found to be similar to the two-stage approach of unsharp masking used here. The parent image was also processed by the present technique defined in Equations (5) and (6). Weight W_2 was set to zero and W_1 to unity. To investigate the simpler method, the diagonal contribution was omitted.

In each image the precise centre of the plastic insert to the phantom was located. Starting from the centre, radial annuli 1 pixel wide were analysed to provide mean and standard deviation values in each. Correct identification of the insert centre was monitored using the standard deviation consistency between annuli which were expected to be similar. The signal strength is given by the pixel values at the plastic water equivalent interface. Plots of this for three cases are shown in Fig. 2. The average of the standard deviations of each of the annuli is used to estimate noise and so allow a signal-to-noise ratio to be estimated for each image. The radial technique was used to improve the reliability of estimated values by both increasing sample size and accounting for more than one dimension. Results are presented in Table I.

By examining Fig. 2 it can be seen that the proposed form of processing yields a better signal-to-noise ratio than the unsharp mask technique. The peak signal is well removed from the accompanying noise background, unidirectionally, so leaving the insert edge artefact reduced and spatially less smeared than the subtraction example. The latter demonstrates the destruction of signal content by the subtraction process, with the peak signal closer to the noisy background. Misregistration is minimised by the alternative differencing method and the stepping features are less confusing than the ringing artefacts from unsharp masking. Even by relaxing the definition of signal amplitude to one of peak to peak, the signal-to-noise ratio for the unsharp mask case is marginally worse.

Whilst statistical differencing and weighted unsharp masking attempt to control noise by selective weighting, it is, of course, possible to improve signal strength, leaving noise levels unchanged. This is the case here; both processing methods produce similar pixel noise levels but the present technique generates an improved signal.

It, therefore, seems that the proposed alternative to subtraction has not only the potential to improve images, in terms of both signal-to-noise ratio and ringing artefact reduction, but will also be computationally faster.

IMPLEMENTATION

The suggested algorithm was developed on a 32 k Data General S130 minicomputer, normally used as a radiotherapy treatment planning computer. Current run times for processing entire images in the extended form below and redisplaying to monitor are less than 20 s. However, coding of the technique on a commercial system for general CT use has been completed and enables near real-time interaction via array processor architecture.

Equations (4) and (5) are implemented in full. Density segmenting by thresholding is presented as two requests to users. These allow the operator to specify a

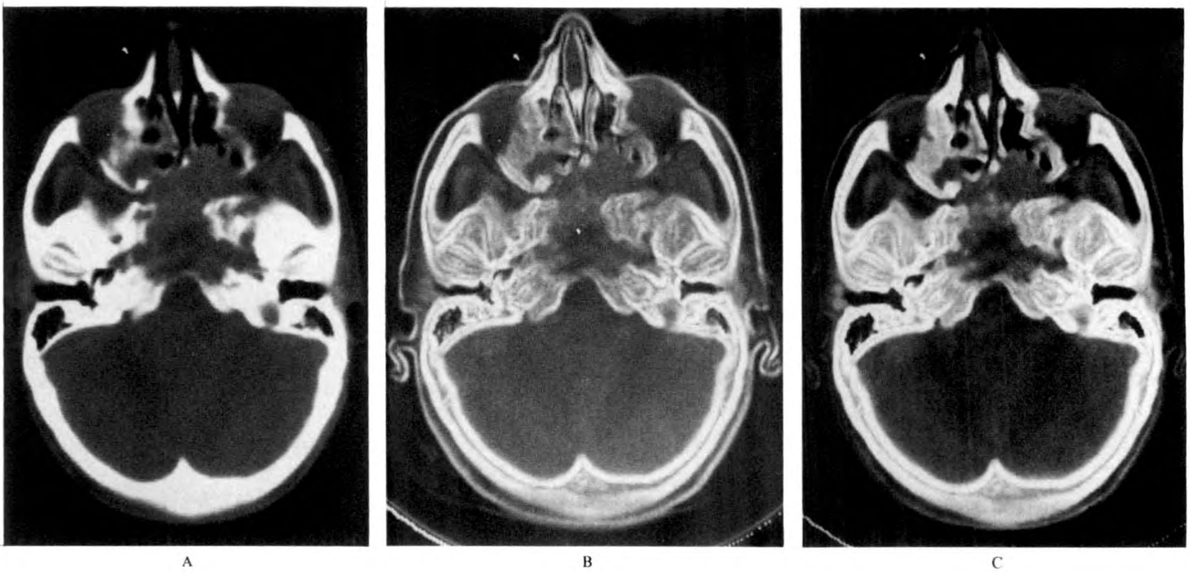

FIG. 3.

Orbito-meatal CT cross-section (L+250, W800). (A) Normal presentation. Note eroding disease. (B) Bony areas processed with preserved soft tissue. (C) Bony areas processed with emphasised soft tissue.

single pixel range that is preserved for display and optionally included or excluded from processing. The weights W_1 and W_2 are presented as requests for an "edge detail boost factor" and "original image contrast factor", respectively. The latter can be fractional and allows the reproduction of unmodified parent image contrast as an aid or cue to tissue identification in edge enhanced images.

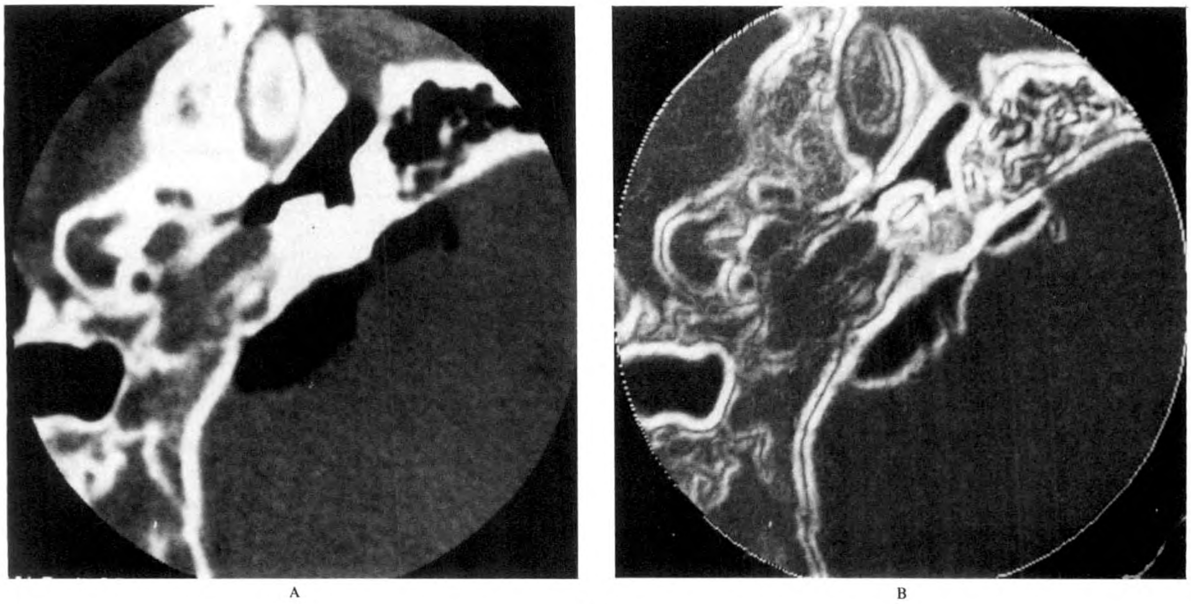

FIG. 4.

Zoom reconstruction of inner ear after gas injection (L+250, W800). (A) Normal presentation. (B) After enhancement: note auditory nerve.

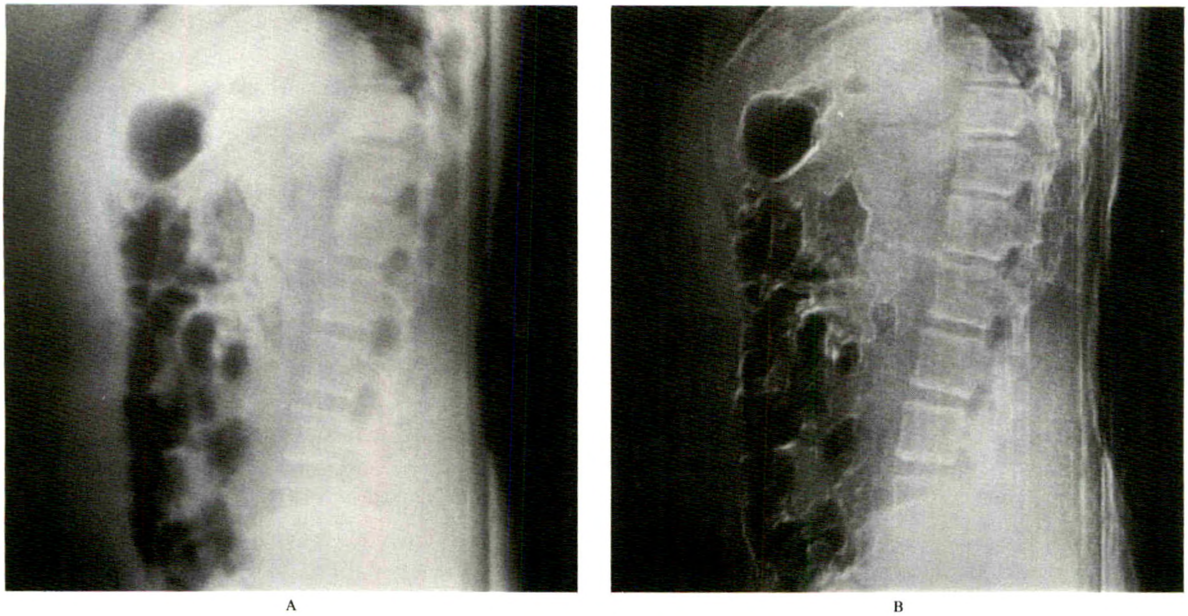

FIG. 5.
Lateral, digital scan projection radiograph (L+250, W800). (A) Normal presentation. (B) After enhancement.

CLINICAL RESULTS

Figure 3A is a cross-sectional scan along the orbitomeatal line, showing temporal bone erosion which would normally be seen by using a narrow window width and varying the window level. Figures 3B and 3C show the result of processing with the method suggested in this paper. Figure 3B shows the erosion and detail in the bony areas alongside preserved soft-tissue features. Figure 3C demonstrates the ability to improve soft-tissue contrast in addition to extracting bony detail.

Gas cisternography

The study of inner-ear disease is a particular case for the application of enhancement solutions to clinical problems. Hanafee et al (1980) in their papers indicate that better software solutions are needed and Shaffer et al (1980) demonstrate the application of spatial filtering for temporal bone studies. Figure 4A shows a zoom reconstructed area of an inner ear, CT section after gas injection. With extreme windowing or conventional subtraction processing the auditory nerve endings can be located but clear visualisation of many features is difficult. Figure 4B shows the result of processing the image by the suggested alternative. A fractional proportion of the parent image has been retained as an aid to characterisation. Measurements across the nerve endings in this and the unsharp mask version confirm the signal-to-noise ratios already demonstrated. This is to be expected since unsharp masking can produce images with an extremely small pixel range and emphasised noise content.

Digital scanned projection radiography

While of peripheral interest in clinical diagnosis, many complex methods for improving DSPR images have been presented in the literature. Figure 5A depicts a lateral DSPR of the spine before processing. Figure 5B is the result after processing with clearly improved edge and contrast detail. A particular application is in the improvement of edge detail for measurement.

CONCLUSION

An alternative and simple method for improving edge and contrast detail in CT images has been presented. While more elaborate and mathematically elegant enhancement routines are available, these tend to offer improvements that prove computationally expensive and time-consuming. It is felt that the solution offered here is effective and stands up favourably to objective comparison with the more common technique of unsharp masking. For inner-ear studies the method appears to be very competitive and wider application to orbital sections and, perhaps, DSPR imaging is a possibility.

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Oedema of the neck after ablation of the thyroid with radioactive iodine

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ABSTRACT

Six out of 30 patients who underwent thyroid ablation with ^{131}I during the period 1975–85 developed acute oedema of the neck within 48 h of the therapeutic dose. The condition was painless and responded well to treatment with corticosteroids. The early onset and absence of pain distinguish this complication from radiation thyroiditis. Dosage calculations and thermoluminescent-dosemeter measurements of the dose at various points on the anterior surface of the neck of a patient with a toxic adenoma of the thyroid treated with ^{131}I were in fairly good agreement with one another and confirmed that the oedema of the neck could not be a direct effect of irradiation on the extrathyroidal tissues. It is suggested that this phenomenon may be a hypersensitivity reaction associated with massive destruction of thyroid tissue.

The destruction of normal thyroid tissue by radioactive iodine (^{131}I) is commonly accompanied by radiation thyroiditis. The majority of patients undergoing this treatment have had a so-called total thyroidectomy, in which case the amount of remaining thyroid tissue is small and symptoms from radiation thyroiditis are likely to be trivial. If, however, one lobe or more has to be ablated, more severe symptoms can be expected. The patients described here had, in addition to radiation thyroiditis, acute oedema of the neck after an ablative dose of ^{131}I.

CASE REPORTS

Case 1.

A woman aged 25 years had a right lobectomy for a papillary carcinoma of the thyroid in December 1975. A scan done post-operatively showed a normal left lobe with, in addition, some activity in the region of the upper pole of the right lobe. The amount of thyroid tissue was estimated to be 15 g. Thyroid uptake at 24 h was 38%. She was given a therapeutic dose of 3.77 GBq (102 mCi) of ^{131}I on January 15, 1976. Two days later she developed acute oedema and inflammation of the subcutaneous tissues on both sides of the neck. She was given intravenous hydrocortisone and prednisone by mouth. The swelling and inflammation resolved. She subsequently had some pain on the left side of the neck but this was not severe. The radiation dose to the thyroid was estimated to be 125 000 cGy. Tests done 3 months later showed no residual functioning thyroid tissue in the neck.

Case 2

A woman aged 68 years had a partial left thyroidectomy for a moderately differentiated carcinoma of the thyroid in October 1978. A scan done post-operatively showed a normal right lobe and about one third of the left lobe still *in situ*. The amount of thyroid tissue was estimated to be 20 g. Thyroid uptake at 24 h was 24%. Three weeks later she was given a further test dose of ^{131}I, having received 5 units of thyroid-stimulating hormone (TSH) the previous day. Thyroid uptake was 54%. A therapeutic dose of 3.42 GBq (92.5 mCi) of ^{131}I was given on November 21, 1978, 24 h after a second injection of TSH. Two days later she developed a massive swelling of the front of the neck (Fig. 1), a hoarse voice and a tight feeling in her throat. She had no pain or stridor. She was given 100 mg of hydrocortisone intravenously and dexamethasone 4 mg four times daily, which was continued for 5 days. The swelling subsided and she was discharged from hospital 6 days after she had been given ^{131}I. She had only minor symptoms of radiation thyroiditis. The radiation dose to the thyroid was estimated to be 135 000 cGy.

Case 3

A man aged 44 years had a right lobectomy for a well differentiated follicular carcinoma of the thyroid in November 1979. A scan done post-operatively showed the remaining left lobe. The amount of residual thyroid was estimated to be 15 g. Thyroid uptake at 24 h was 29%. He was given 5 units of TSH 6 h before being given a therapeutic dose of 2.85 GBq (77 mCi) of ^{131}I on November 27, 1979. Two days later he developed painless swelling involving both sides of the neck and the submental region. He was treated with prednisolone which was tailed off over a period of 6 days. On the seventh day his throat became very painful and he had pain referred to the left ear. There was tenderness over the left lobe of the thyroid. The findings were characteristic of severe radiation thyroiditis. The swelling on the front of the neck, however, was subsiding. He was treated with intravenous hydrocortisone and prednisolone by mouth. The thyroiditis subsided within a week.

The radiation dose to the thyroid on the basis of a 29% thyroid uptake would have been 74 000 cGy. The TSH is likely to have increased the thyroid uptake to about 50% and this would have resulted in a corresponding increase in the radiation dose to the thyroid.

Tests done 3 months later (February 27, 1980) showed a small area of functioning thyroid tissue in the midline just above the suprasternal notch. This activity did not correspond to the activity seen in the first scan and it was concluded that it was probably located in tumour which had escaped any significant damage from the first treatment. Thyroid uptake was about 0.5%. He was given a further therapeutic dose of 7.03 GBq (190 mCi) of ^{131}I without incident. Tests done 3 months later showed no functioning thyroid tissue in the neck or elsewhere.

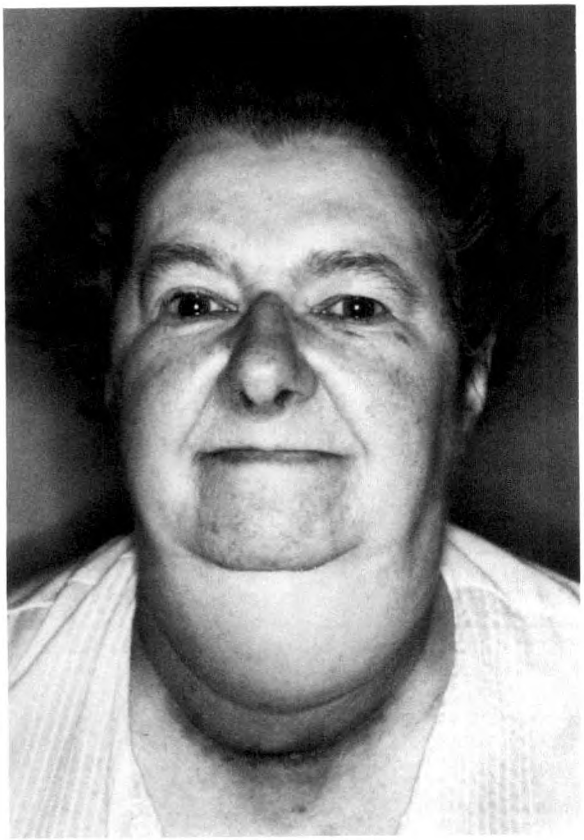


FIG. 1. *Case 2.*
Oedema of the neck.

Case 4

A man aged 58 years had a lump removed from the lower pole of the right lobe of the thyroid in January 1980. Histological examination of the specimen showed a papillary carcinoma of the thyroid. A scan done post-operatively showed a normal right lobe with some activity in the upper pole of the left lobe. The amount of thyroid was estimated to be 20 g. Thyroid uptake at 24 h was 12%. He was given 10 units of TSH intramuscularly and 24 h later, on May 3, 1980, a therapeutic dose of 3.7 GBq (100 mCi) of ^{131}I. Two days later he complained of neck swelling and a choking sensation. On examination he had considerable swelling of the neck which extended up to the level of the mandible on both sides. He was treated with hydrocortisone intravenously and dexamethasone intramuscularly. The following day he still had swelling of the neck and face but no pain or discomfort. By the time he was discharged from hospital on May 8, 1980 the swelling had more or less resolved.

He had to be readmitted on May 14, 1980 because he had developed palpitations, effort dyspnoea and retrosternal pain. He also had some pain in the neck. Steroids had been discontinued on discharge from hospital. On examination there was found to be some tenderness of the neck. He had a sinus tachycardia with a pulse rate of 120 min^{-1} and was thought to be hyperthyroid. This diagnosis was subsequently confirmed by the finding of a serum thyroxine level of 180 nmol/l (normal range 78–142 nmol/l). The following day he developed atrial fibrillation. An electrocardiogram showed left bundle branch block and evidence of left ventricular enlargement. He was treated with propranolol and digoxin and made a satisfactory recovery. The radiation dose to the thyroid in this patient would have been 30 000 cGy on the basis of a thyroid uptake of only 12%. The TSH is likely to have at least doubled the thyroid uptake and, hence, the radiation dose.

Case 5

A man aged 61 years had a left thyroid lobectomy performed on November 21, 1984. Histological examination showed a follicular carcinoma of the thyroid. A scan done post-operatively showed thyroid tissue on the right side in an area corresponding to the right lobe. The amount of thyroid tissue was estimated to be 10 g. Thyroid uptake at 24 h was 39%. He was given a therapeutic dose of 2.92 GBq (79 mCi) of ^{131}I on February 12, 1985. Three days later he developed oedema of the whole of the front of the neck and, subsequently, radiation thyroiditis on the right side. This was not considered sufficiently severe to need steroid therapy. Two weeks after the ^{131}I therapy there was some tenderness over the right lobe and he had a sinus tachycardia suggestive of hyperthyroidism but these signs had disappeared a week later. Tests done 3 months later showed no functioning thyroid tissue in the neck.

The estimated radiation dose to the thyroid in this patient was 105 000 cGy.

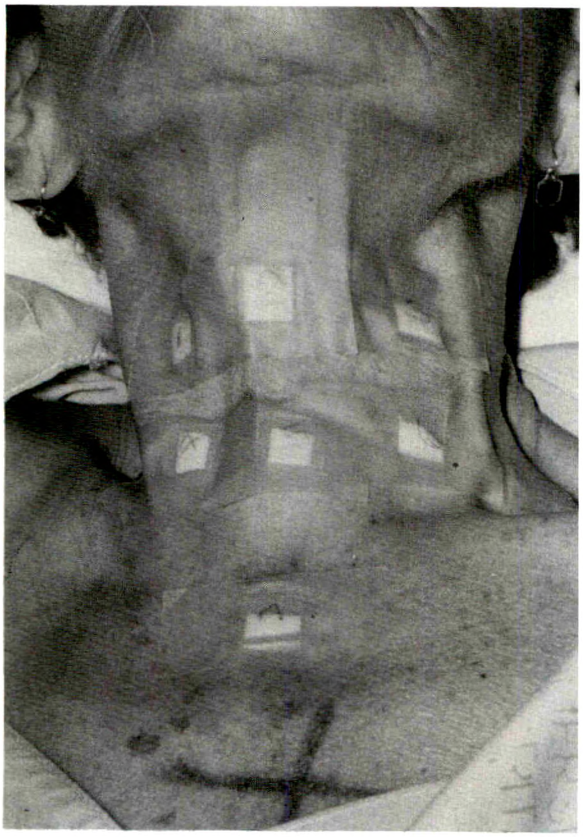
Case 6

A man aged 62 years had a tumour arising in the right lobe of the thyroid removed on January 31, 1985. Histological examination of the specimen showed an oxyphil follicular (Hürthle cell) carcinoma of the thyroid. A scan done post-operatively showed a normal left lobe and another small area of functioning thyroid tissue on the right side. The amount of thyroid tissue was estimated to be 20 g. Thyroid uptake at 24 h was 32%. He was given a therapeutic dose of 2.89 GBq (78 mCi) of ^{131}I on February 26, 1985. Within 48 h he had developed submental oedema but there was no pain or tenderness of the thyroid. He subsequently did develop evidence of radiation thyroiditis which was not of sufficient severity to warrant steroid therapy. He was also mildly hyperthyroid with a serum T_4 of 178 nmol/l. The submental oedema subsided within about a week. Tests done three months later showed no functioning thyroid tissue in the neck.

The radiation dose to the thyroid was estimated to be 67 000 cGy.

RADIATION DOSE TO EXTRATHYROIDAL TISSUES

The gamma-ray dose to extrathyroidal tissues has been measured in a patient with a toxic adenoma of the thyroid who was treated with ^{131}I. The patient, who had a thyroid uptake of 80% and who was estimated to have 5 g of functioning thyroid tissue, was given a therapeutic dose of 740 MBq (20 mCi) of ^{131}I. From the point of view of radiation dosimetry, the conditions were very similar to those of a patient having thyroid tissue ablated after a thyroidectomy. It is estimated that the thyroid adenoma would have received a total radiation dose of about 150 000 cGy, of which 40% (60 000 cGy) would have been delivered within the first 48 h, the critical period in the patients who developed oedema of the neck.



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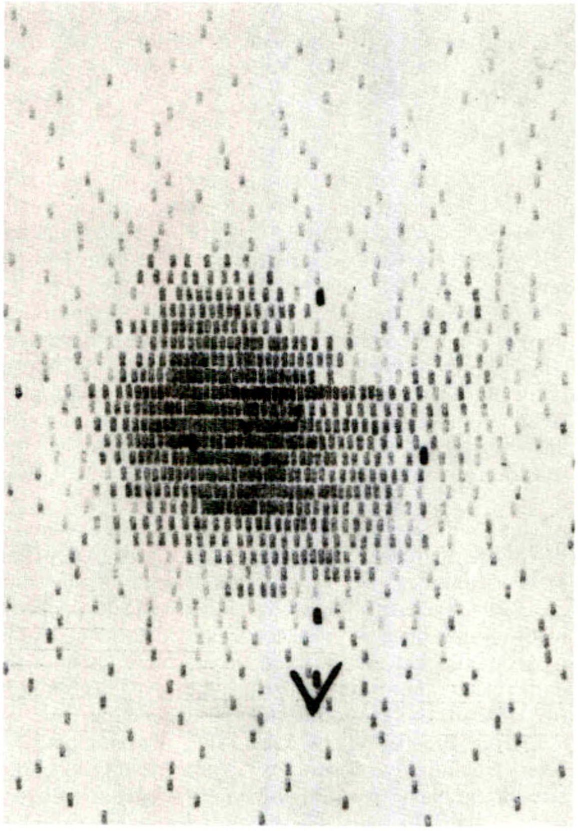

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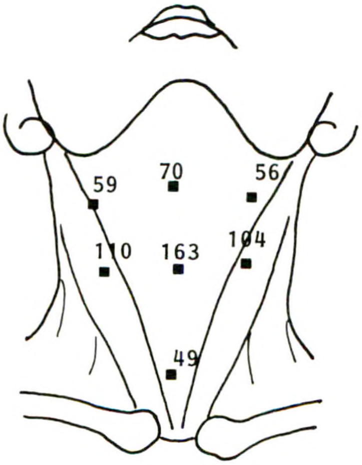
FIG. 2.

(A) Location of TLD sachets in a patient with a toxic adenoma of the thyroid. (B) Radiation doses recorded over a period of 48 h in the same patient. (C) Rectilinear scan showing area of functioning thyroid tissue in the same patient.



B

Thermoluminescent dosemeters (TLDs) were used to measure skin doses on the anterior surface of the neck. The dosemeters were in the form of 1 cm × 1 cm nylon sachets each containing 50 mg of LiF powder. Seven sachets were taped to the front of the neck as shown in Fig. 2A and were left in position for 48 h. The resultant doses shown in Fig. 2B ranged from 163 cGy to 49 cGy. The dose pattern correlated well with the distribution of activity displayed in the scan in Fig. 2C. The TLD doses were derived from a calibration curve obtained from measurements using a 0.1 cm^3 ionisation chamber on a neck phantom containing a known activity of ^{131}I.

These measured gamma-ray doses are minimum figures since they were obtained at the skin surface. There will be a significant increase in dose at points in the neck tissues deep to the skin. Calculations show the doses over 48 h at 1.0 cm and 2.5 cm from the surface of a sphere of radius 1.0 cm containing 592 MBq (16 mCi) of ^{131}I with an effective half-life of 3.25 days to be 360 cGy and 110 cGy, respectively (Freedberg et al, 1952; Hine & Brownell, 1956).

DISCUSSION

Radiation thyroiditis is characterised by pain and localised tenderness of thyroid tissue. It normally develops about 3 or 4 days after ^{131}I has been given but it may occur after a longer interval. The symptoms, if severe, may be relieved by treatment with a corticosteroid. Another, often unrecognised, complication of thyroid ablation is transient hyperthyroidism which is precipitated by massive destruction of thyroid tissue and consequent release into the circulation of large amounts of thyroid hormone. This complication may be avoided if the thyroid gland is first depleted of its store of hormone by treatment with an antithyroid drug.

The condition described here differed from radiation thyroiditis in that it was painless and appeared within 48 h of treatment. All six patients also had evidence of radiation thyroiditis which developed after the oedema of the neck and was probably modified to some extent by previous treatment with corticosteroids. Three of the patients had clinical evidence of hyperthyroidism and in two of them this was confirmed biochemically.

During the period 1975 to 1985, 30 patients have been given ablative doses of ^{131}I. In a few this was done as a preliminary to the treatment of metastatic disease with ^{131}I but in the majority it was intended to ablate residual normal thyroid tissue in patients who had had a thyroidectomy for a differentiated carcinoma of the thyroid. There was wide variation in thyroid mass (1 g to 20 g) and in thyroid uptake (1% to 50%). The estimated radiation dose also varied considerably with values between 50 000 cGy and 150 000 cGy. It would seem, from examination of the data, that the common features in the patients who developed oedema were a substantial mass of thyroid tissue (10 g or more) and a fairly high radiation dose. There is uncertainty about the radiation dose in two of the patients who were given TSH before the therapeutic dose but it is a reasonable assumption that all patients received a dose in excess of 50 000 cGy and that five of them received a dose in excess of 100 000 cGy. Severe reactions are likely to be encountered with the latter dose.

A search of the literature has revealed only one other account of acute oedema of the neck occurring in patients treated with ^{131}I for thyroid carcinoma (Hoschl et al, 1965). Some of the 17 patients who developed this complication (13% of the total number treated) were given very large doses of ^{131}I. It was pointed out that the condition differed from radiation thyroiditis by its earlier appearance and by the absence of pain. Respiratory distress was quite common and in some patients was thought to be life-threatening. Treatment with corticosteroids was found to be of benefit.

It is difficult to provide an explanation for the phenomenon described here. Chronic lymphoedema of the neck may be seen in patients who have had high-dose radiotherapy to this region, particularly when this is given after surgery. The mechanism here is presumably damage to normal lymphatic pathways. Due to the limited range of the beta particles the radiation dose from ^{131}I is largely confined to the thyroid gland itself. Calculations and measurements carried out on a patient suggest that the radiation dose to the tissues in the vicinity of the thyroid is unlikely to exceed 400 cGy in the first 48 h. It is highly unlikely, therefore, that the oedema can be ascribed to a direct effect of irradiation on perithyroidal tissues. Some alternative explanation has to be sought.

It would seem that neck oedema is liable to occur whenever there is massive destruction of thyroid tissue. This process is accompanied by release into the circulation of thyroid hormones, thyroglobulin and a variety of degradation products. The clinical features of early neck oedema following ^{131}I ablation of the thyroid are very similar to those of so-called angioneurotic oedema. The rapidity of onset, lack of pain and occasional stridor suggest an allergic response rather than a direct radiation effect. It is possible that in some way a Type-1 hypersensitivity reaction might be involved in the pathogenesis of this condition.

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Late radiation response of kidney assayed by tubule-cell survival

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ABSTRACT

An assay for the survival of renal tubule cells was developed using mice. It is analogous to other *in-situ* clonogenic cell survival assays. One kidney was irradiated using a ^{137}Cs irradiator and removed 60–68 weeks later for histological examination. In unirradiated animals there were about 370 tubules in contact with the capsule in a coronal cross section at the middle of the kidney. After irradiation, extensive tubular damage was the dominant lesion. The number of epithelialised tubules in contact with the capsule showed a dose-dependent logarithmic decline. The dose–survival relationship for the clonogenic cells responsible for the regeneration of tubule epithelium was described by a D_0 value of 1.5 Gy over the dose range 11–16 Gy. This radiosensitivity resembles that of stem cells in acutely responding tissues. The lack of histological evidence of damage to the arterial vasculature at the time the tubules are initially denuded of epithelium, and the similarity of renal tubule cell radiosensitivity to that of other mammalian cells, support the hypothesis that "late" radiation injury results primarily from depletion of parenchymal cells, not indirectly from injury to blood vessels, as has been the prevailing belief.

Tissue responses to radiation develop at widely different rates and have been grouped into those appearing within about 6 weeks of exposure (acute effects) and those which appear only months, or even years, after irradiation (late effects). Examples of tissues which show an early response to a given dose of radiation are bone marrow, skin epithelium, gastrointestinal mucosa and spermatogenic epithelium, while examples showing a slow response include kidney, central and peripheral nervous systems, endocrine glands, dermis and the musculoskeletal system.

The distinction between early and late effects is of importance for several reasons.

(i) Acute effects appear during a course of radiotherapy lasting several weeks and, if too severe, can be modified by protracting the treatment. Late effects appear long after a routine course of radiotherapy is completed and, hence, cannot be used to individualise a dose prescription. Therefore, there exists a greater need for prospective knowledge of dose–response relationships for late-responding tissues than for acutely responding tissues.

(ii) The responses to dose fractionation of early- and late-responding tissues are consistently different from one another (Withers et al, 1982, 1983; Thames et al, 1982; Barendsen, 1982). Until now, multifraction dose–response characteristics of late-responding tissues have been measured *in situ* only by assaying tissue function, whereas for early-responding tissues there exist assays of cell survival as well as of tissue function (Withers, 1983). The nature of the difference in fractionation response between acutely and slowly responding tissues would be better understood if the multifraction dose survival characteristics of the target cells for late injury could be measured and compared with those based on end-points of function.

(iii) It is generally accepted that acute irradiation effects result from sterilisation of parenchymal cells (Quastler, 1956). This view is reasonable because a logarithmic decline in cell survival with increasing radiation dose, which is characteristic of cells irradiated *in vitro*, has been demonstrated *in situ* for many acutely responding tissues (Potten & Hendry, 1983, 1985) and because cellular isosurvival has been correlated with a tissue isoeffect (Hendry et al, 1983), regardless of the fractionation pattern (Withers & Elkind, 1969; Meistrich et al, 1978), or quality of radiation (Hornsey, 1973) to which the animals were exposed. In contrast, the prevailing concept of the pathogenesis of late effects is that they result from various injuries to blood vessels (Gabriel, 1926; Rubin & Casarett, 1968; Lindop et al, 1970; Casarett, 1976; Hopewell, 1980; Law, 1981). However, an alternative view is that late responses, like acute responses, represent loss of the reproductive integrity of parenchymal cells (Schulz & Hoffman, 1905; Willis & Bachem, 1927; Bolliger & Laidley, 1930; van den Brenk, 1971; Zeman & Samorajski, 1971; Zeman & Soloman, 1971; Withers et al, 1980; van der Kogel, 1980). Since death of cells after irradiation is usually linked to their progression through the mitotic cycle (Thompson & Suit, 1969), acute responses would be expected to appear in tissues whose cells turn over quickly and late responses in those whose cells turn over slowly (Withers et al, 1980). The epithelium of the renal tubule turns over slowly (Cuppage & Tate, 1967; Phillips and Leong, 1967; Cuppage & Tate, 1968) and is capable of regenerating after cytotoxic injury (Oliver, 1915, 1953; Cuppage & Tate, 1967, 1968).

Until now, an *in-situ* dose–survival relationship has not been measured in the parenchymal cell population of any slowly responding tissue, although transplantation assays have indicated that the radiosensitivity of the cells of the liver (Jirtle et al, 1981; Fisher, 1985) and thyroid (Mulcahy et al, 1980, 1984) is similar to that of cells in acutely responding tissues.

This report describes the development of an assay for the survival of parenchymal cells of a characteristically slowly responding tissue, the kidney, and the measurement of a single dose-survival curve. The assay is analogous to *in-situ* clonogenic assays for acutely responding tissues. It especially resembles the one for spermatogenic stem-cell survival (Withers et al, 1974), the major difference being that about 60 weeks were allowed for regrowth of clonally derived colonies in the kidney tubules, compared with 5 weeks for spermatogenic cells.

MATERIALS AND METHODS

Mice

Specific pathogen-free C_3Hf/Kam female mice were entered into experiments at an age of 10–12 weeks. They were housed five per cage, fed sterile food (Wayne Sterilizable Lab Bloc) and sterile acidified water *ad libitum*. Automatic timers were used to maintain a 12 h light–dark cycle.

Irradiations

A specially designed ^{137}Cs small-animal irradiator (Hranitzky et al, 1973) with a 2 cm-diameter collimated field from two parallel opposed beams was used for all radiation exposures. The dose-rate, measured by LiF thermoluminescent dosimeters in a Lucite phantom mouse, was 9.4 Gy/min. Mice were anaesthetised with an intraperitoneal injection of 55 mg/kg Nembutal (sodium pentobarbital; Abbott) and their left kidneys carefully palpated and placed in the centre of the 2 cm-diameter radiation field. The supine mouse was taped in position with the radiation beams directed through its dorsal and ventral surfaces on the left side. A 2 cm-diameter field was chosen as a compromise between the possibilities of geographic misses from using a smaller field and excessive bowel injury from using a larger one. Because it was considered that one normal kidney would be needed to ensure survival of the animal, the right kidney was neither irradiated nor removed, as is sometimes done to stimulate growth in the contralateral, irradiated, organ.

Histology

Mice were sacrificed and their left kidneys removed and fixed in neutral buffered formalin. After routine histological processing, 4 μm coronal cross-sections were cut at the level of the renal pelvis. Sections were stained with haematoxylin and eosin and tubules counted microscopically, usually at 160 × magnification.

Organ shrinkage

The degree of radiation-induced organ shrinkage was assessed by measuring the circumference of the complete cross section using a Prado projection microscope and an Alvin wheel micrometer.

Development of assay

In preliminary experiments, mice were given a range of doses up to 30 Gy and were sacrificed at intervals up to 93 weeks after irradiation. The rate of depletion of renal tubule epithelium was dose-dependent, extensive injury being obvious 32 weeks after 30 Gy but only beginning to appear by about 50 weeks after a dose of 11 Gy. After this variable latent period there is a dose-dependent interval, varying from about 5 weeks to about 15 weeks, during which there is a dramatic change in the histological appearances of the irradiated kidney: a fairly normal-appearing, although shrunken, organ gives way to one showing extensive depletion of the tubule epithelium. This phase of rapid tubule degeneration is followed by a slow sclerosis or disappearance of glomeruli but little apparent further change in the structure of tubules. Comparison of sections taken at intervals beyond 62 weeks yielded fairly constant counts of regenerated renal tubules for a given dose. For example, the percentage of regenerated tubules in contact with the capsule between 63 and 72 weeks, compared with those at intervals greater than 73 weeks after doses of 12.5 Gy, 14.5 Gy and 16 Gy were 23% vs 30%, 4.6% vs 3.2% and 1.75% vs 1.55%, respectively. The numbers of animals in these six groups were 14, five, five, one, two and two, respectively. Accordingly, animals sacrificed between 60 and 68 weeks after radiation were used in determining the dose-survival curve presented in this paper. In later experiments, from which most of the present data were derived, animals were routinely killed at 60 weeks.

Criterion and technique for scoring regenerated tubules

For ease of scoring, a sampling technique was employed whereby only those tubules touching the renal capsule were scored for viability (Hewitt, 1956). An arbitrary criterion for scoring a tubule as fully regenerated was that it looked normal, being lined with well differentiated cuboidal or columnar cells having a large amount of eosinophilic cytoplasm (Fig. 1). Tubules which had not regenerated usually consisted of only an intact basement membrane devoid of epithelium. During the phase of rapid development of histological changes in the tubules, they sometimes contained flattened cells with a small amount of cytoplasm and sometimes, small hypercellular clumps with densely stained nuclei. However, by 60 weeks after doses even as low as 11 Gy, there is a clear segregation of cortical tubule cross-sections into those with no surviving epithelial cells and those completely lined by normal-appearing cells. The criterion used for re-epithelialisation of a tubule was that its circumference be fully surfaced by healthy epithelium, regardless of the number of nuclei in the plane of the section. In serial sections, such tubules show an intact epithelium, in

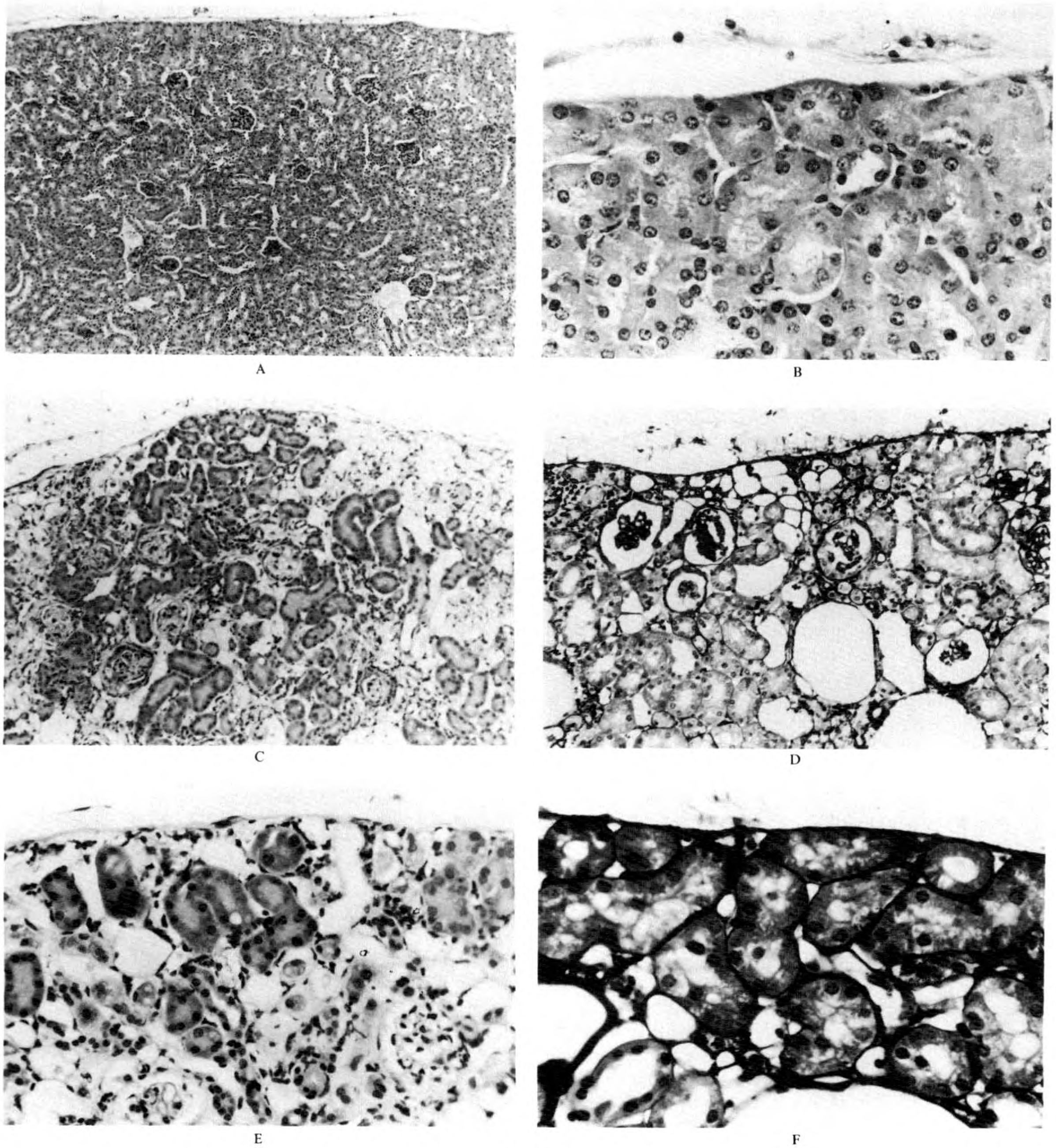

FIG. 1.
Photomicrograph of mouse kidney. (A) Normal, H&E, × 45. (B) Normal, H&E, × 400 showing proximal tubules in contact with capsule. (C) Sixty-eight weeks after exposure to 15 Gy. Note a cluster of five epithelialised tubule cross-sections in contact with the capsule. Some glomeruli appear normal and some are sclerotic. H&E, × 100. (D) Sixty weeks after 12.5 Gy. Note re-epithelialised and depopulated proximal tubules. One glomerulus shows epithelialisation of the outer membrane of Bowman's capsule, a normal phenomenon, especially in male mice; others show various degrees of involution, including complete absence of a glomerular tuft leaving "cystic" spaces. Jones' silver stain (Jones, 1951), × 160. (E) Sixty weeks after 13 Gy. Note normal proximal tubules and glomeruli amid ghosts of de-epithelialised tubules. One epithelialised tubule is in contact with capsule. H&E, × 200. (F) Sixty weeks after 12 Gy. Note that the number of cell nuclei in regenerated tubules varies; in one tubule no cell nuclei are seen, even though it is obviously re-epithelialised and would be scored as such. Jones' silver stain, × 250. All magnification factors are approximate.

contrast to the bare basement membranes of the unregenerated tubules.

Measurement of tubule survival

The number of regenerated tubules in contact with the capsule was scored in two complete coronal histological sections per kidney and expressed as a fraction of the number in similar transverse sections in age-matched, unirradiated controls. The "circumference" with which tubules made contact was essentially only the convex surface: for scoring purposes a cut-off zone was established arbitrarily to be where the capsule gave way to hilar adipose tissue, a site usually also marked by a small artery on the kidney surface. In unirradiated kidneys there was a mean of 370 (±5 SEM) tubules in contact with the capsule, representing about four for each glomerulus in the section. The number of glomeruli per cross section was 91±2 in the unirradiated kidney and 99±5 in eight kidneys exposed to doses high enough to cause maximal loss of tubules and contraction of the organ (15.5–17.5 Gy). The multiplicity of tubule cross-sections per glomerulus and, therefore, per nephron reflects the convoluted course of the tubule through the cortex. In irradiated kidneys, this is apparent as a clustering of regenerated tubules which is most apparent at high doses, since then the clusters are widely separated from one another. In eight mice given doses of 15.5–17.5 Gy, the mean number of tubule cross-sections in those clusters contacting the capsule was 2.2±0.2. That the 370 tubule cross-sections in contact with the capsule represent a smaller number of nephrons is immaterial to the quantification of the dose–survival relationship because the same multiplicity applies to both control and post-irradiation counts.

Correction for contraction

The contraction of the circumference of the organ with dose is shown in Table I. It is uncertain what effect such contraction might have on counts of epithelialised tubules. If the glomeruli and tubules remained constant in diameter within a contracted kidney, the probability of sectioning them should increase. Although some glomerular spaces were dilated, often with a small or missing capillary tuft (Fig. 1), others were smaller than in controls and the mean value for glomerular diameter after various doses was the same as that for controls (Table I). Counts of total tubules per circumference were not made in irradiated kidneys because the depopulated tubules are collapsed to varying degrees and their recognition is sometimes uncertain. Although regenerated tubules in irradiated mice look larger than normal, this is an illusion created by the collapse of depopulated tubules, the mean diameter actually being less (Table I).

Ultimately, the decision was made that no corrections for dose-dependent changes in renal architecture would be attempted. The basis for the decision was that, over the dose range of interest, the changes are small (Table I). On the other hand, comparison of data in Table I and Fig. 1 shows that the relatively large tubule and glomerulus cross-sections in the kidneys receiving 14 Gy are associated with a data point displaced above the survival curve.

Estimating tubule-cell survival

The proportion of regenerated tubules decreased logarithmically as a function of dose. The slope of the curve relating the logarithm of tubule survival to dose was similar to that for mammalian cells in conditions where it is known that the assay measures the independent survival of single cells (Hewitt & Wilson, 1959; Becker et al, 1963; Elkind & Whitmore, 1967). Therefore, as with other *in-situ* clonal survival assays (Potten & Hendry, 1983, 1985), it is unlikely that a multiplicity of cells is necessary for regeneration of all or part of a tubule. This question is further discussed in the Appendix. It may be assumed that tubules devoid of epithelium contained no surviving epithelial clonogens, at least within the vicinity of that cross-section. When a proportion of the tubules, or tubule segments, is completely depopulated (zero surviving clonogens), those that regenerate must do so from small (randomly distributed) numbers of cells. At high doses, when few tubules regenerate, most would have been derived from a single clonogenic cell. At lower doses a proportion of tubules would have regenerated from two, or even more, randomly and independently surviving cells and so the *average* multiplicity of surviving cells per regenerated tubule (or subunit) could be slightly greater than unity. As has been done with other *in-situ* clonogenic cell-survival end-points (Withers, 1967; Withers & Elkind, 1970; Chen & Withers, 1972; Withers & Mason, 1974; Withers et al, 1974; Potten &

TABLE I

EFFECTS OF IRRADIATION UPON THE KIDNEY, COMPARED WITH NORMAL CONTROLS (MEANS ± SEM)

	Tubule survival (no Poisson correction)	Tubule diameter (μm)	Glomerulus diameter (μm)	Kidney circumference (mm)	% Lethality (60 weeks)
Normal	370± 5 (tubules)	33±0.9	77±0.6	16.95±0.34	–
12.5 Gy	108±15 (tubules)	24±1.1	79±1.8	11.8 ±0.41	35%
14.0 Gy	65±10 (tubules)	30±1.8	82±1.8	11.2 ±0.28	53%
15.5 Gy	17± 7 (tubules)	26±0.4	78±3	10.4 ±0.55	69%

Hendry, 1983, 1985), the multiplicity of surviving cells was accounted for, using Poisson distribution statistics. The survival curve for clonogenic cells obtained after the Poisson correction is slightly steeper than that for tubule survival.

RESULTS

Mouse mortality

During a 70-week period after irradiation with 11–15.5 Gy, about 40% of the irradiated mice died. Representative death rates are shown in Table I. The cause of death was not usually established. Some animals developed "spontaneous" tumours outside the direct radiation field, some developed tumours in the radiation field, some died with late radiation damage of the bowel, including adhesions, constrictions, obstructions and perforations, usually located near the caecum (outside the radiation field). However, most animals were found dead and, because of their rapid autolysis, no cause for their death was established. The dose-dependent mortality introduces some uncertainty into the accuracy with which renal tubule radiosensitivity is measured from our experiments to date.

Histological changes

The microscopic appearances of kidneys irradiated 15 months earlier are contrasted with those of a control in Fig. 1. In the irradiated organs, normally epithelialised convoluted tubules are distributed among the ghosts of tubules completely depopulated of epithelium. As tubule depletion becomes more extensive with increasing dose, clustering of "surviving" tubules becomes more apparent.

Glomeruli in irradiated kidneys usually appear normal at 60 weeks after doses of 11–16 Gy, but sometimes they have shrunk to a small, although well vascularised tuft and sometimes they are not to be seen, leaving only an empty Bowman's capsule which could be mistaken for a cyst or a dilated tubule.

Renal tubule-cell radiosensitivity

A single dose–survival curve for renal tubule epithelial cells is presented in Fig. 2. It is characterised by a D_0 value of 1.53 Gy (1.25–1.98 Gy, 95% confidence limits). The data from five different experiments are pooled. The total number of animals from which data became available was 162. The number of animals per data point ranged from 24 to four: for the eight doses between 11 Gy and 14 Gy there was an average of 17 animals per point and for the four doses between 14.5 Gy and 16 Gy there was an average of six, reflecting the higher mortality after higher doses (Table I). There was considerable variation in counts between mice and between experiments.

As discussed in the Appendix, this observed value for D_0 is similar to D_0 values measured for mammalian cells in conditions in which a single-cell origin of regenerated colonies can be proven (Hewitt & Wilson, 1959; Becker et al, 1963; Elkind & Whitmore, 1967) and, since it is unlikely that the "true" value of D_0 for renal tubule cells is greater by a factor of 2 or more, it is unlikely that two or more surviving cells/tubule are necessary for regeneration (see Appendix).

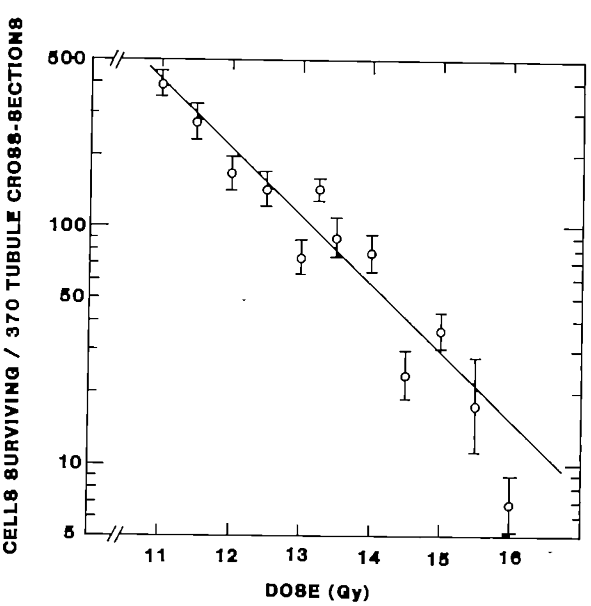

FIG. 2

Dose–survival curve for tubule-regenerating cells. Error bars are standard errors of the means. The curve is a weighted linear regression. The mean lethal dose (D_0), which is the dose that results in the random reduction of survival to 37% (e^{-1}), is 1.53 Gy (1.25–1.98 Gy, 95% confidence limits)

DISCUSSION

Histology

The structural changes in irradiated mouse kidney resemble those published by others (Schulz & Hoffman, 1905; Gabriel, 1926; Willis & Bachem, 1927; Phillips & Ross, 1973), although their rate of development is slower than in the dog (Bolliger & Laidley, 1930; Hoopes, 1984). The time of scoring regenerated tubules must, therefore, be determined if the assay is to be established in different species. In areas of tubular necrosis, or, more correctly, apoptosis (Kerr et al, 1972), residual epithelial cells assume a simpler embryonic form while dividing and relining the damaged tubule, returning gradually thereafter to a differentiated, mature epithelium. If the nephron is not reconstituted by regeneration of the tubule epithelium it atrophies and the glomerulus ultimately involutes or undergoes sclerosis. If there is extensive loss of nephrons, the arteries ultimately show contraction and thickening of the media and intima, a change that is probably due, at least in part, to the contraction of the organ as a whole (Bolliger & Laidley, 1930).

Clonal origin of regenerated tubules

It has been assumed that the focally distributed epithelialised tubules seen in histological sections 60 weeks after irradiation (Fig. 1) were regenerated from single surviving cells. A reviewer questioned why the normal-appearing tubules may not merely have persisted after irradiation, and not been regenerated. Accepting that radiation kills cells randomly (as further evidenced by the survival curve in Fig. 2) and that there are approximately equal (logarithmic) numbers of cells in the renal tubules that make contact with the capsule of the kidney at some point(s) in their convoluted course, it is inherently unlikely, on probabilistic grounds, that normal-appearing multicellular tubules would be seen surviving side by side with completely denuded ones unless they were regenerated from small numbers of surviving cells, usually one.

However, three conditions which would possibly lead to persistence rather than regeneration of tubules can be considered: a wide variation in cellular radiosensitivity, a dose-dependent variation between tubules in their rate of development of injury, or that tubules survive or die as whole units because their death is determined by blood vessel injury.

Variation in tubule sensitivity. If the tubule epithelial cell radiosensitivity varied widely among tubules, some would be lost at low doses but the survival at high doses would be progressively more determined by the response of the most radioresistant cells. However, the data are not consistent with this interpretation since there was no bend in the curve to suggest that there existed an especially radioresistant subpopulation of tubules: rather, the data show consistency of response.

Variation in the rate of development of injury. If the histological picture at 60–68 weeks after a range of doses represented merely the persistence of well epithelialised tubules among others completely depopulated, the curve in Fig. 2 would represent a "dose–persistence" curve. Although the number of animals used was small, a pilot experiment for those reported here indicated that, after various doses, there was a rapid decline in counts of surviving tubules, but that this was followed by a plateau phase during which tubule counts stabilised (see Materials and Methods): a "persistence" hypothesis should predict a continuing dose-related decline. Furthermore, to construct a dose persistence curve would demand scoring at different, dose-related times after irradiation, whereas the curve in Fig. 2 was derived from observations over a narrow time-span, and mostly at one time, 60 weeks.

Vascular catastrophe. It is possible that a large population of tubule cells could survive or be lost as a unit if their viability depended upon the integrity of a blood vessel. If blood-vessel integrity depended upon cells whose survival response was defined by a D_0 value of 1.5 Gy (in a manner denied the renal tubule in such an argument), then healthy-appearing tubules could "persist" or be lost as units, giving a dose-dependent decline in focally distributed viable tubules (Fig. 1). However, since the afferent arteriole supplying the glomerulus becomes the efferent arteriole supplying more than one tubule after traversing the glomerular capillary network (Fourman & Moffat, 1971), it is difficult to postulate a mechanism whereby several efferent arterioles are sufficiently damaged to eliminate all tubular epithelium whilst the afferent arterioles and the glomeruli appear unaffected at the time of development of tubule injury.

Glomerulosclerosis was extensive in the mouse kidneys studied at later times in the present experiments, *e.g.* at 80–90 weeks, and arterial thickening could then be seen with increasing frequency. Although radiation may have played some direct role in their development, these later-developing changes appear to be secondary to tubular atrophy and kidney shrinkage.

An argument advanced in support of a vascular origin of radiation nephritis is that the extraction of rubidium 86 is reduced 4–12 months after irradiation (Glatstein et al, 1975). Extraction of rubidium is a process determined not only by blood flow but also by renal tubular function. Although at early times after irradiation, tubules are not sufficiently depopulated of epithelial cells to detect the histological changes seen at 60 weeks, a progressive loss of kidney weight with time reflects the process. If it is assumed that tubule epithelium constitutes about 60% of the weight of normal mouse kidney and that renal weight loss results only from loss of this epithelial lining, the dose- and time-related weight losses recorded by Glatstein et al (1975) provide a reasonable correlation between loss of tubule epithelium and decrease in ^{86}Rb extraction (Table II).

In summary, radiobiological principles indicate that the normal-appearing tubules distributed throughout irradiated kidneys (Fig. 1) are clonally derived (see Appendix). This is the simplest hypothesis and it is consistent with widely accepted concepts of the pathobiology of radiation injury in other tissues. In our opinion, no plausible vascular mechanism has been advanced to explain the tubule degeneration observed histologically.

Radiation response

Although the slope of the curve in Fig. 2 indicates that the radiosensitivity of cells that regenerate the tubule of the nephron is similar to that of cells of the epithelium of the gastrointestinal tract (Withers & Elkind, 1970; Chen & Withers, 1972; Withers & Mason, 1974), spermatogenic tubules (Withers et al, 1974), growing cartilage (Kember, 1967) and skin (Withers, 1967; Emery et al, 1970), the rates of response of these various tissues are quite different from one another. Thus, in the mouse, the time required for depletion of the epithelium after a single dose of about 14 Gy of X irradiation is of the order of 3 days in the jejunum, 5 days in the colon, 10 days in the stomach, 12–24 days in the skin, 30 days in the seminiferous

TABLE II

CORRELATION OF ^{86}Rb EXTRACTION AND TUBULE EPITHELIAL LOSS USING DATA FROM TABLE II OF GLATSTEIN ET AL (1975)

Dose (Gy) and No. of fractions	Assay time (months)	% of control Rb extraction	% of control tubule epithelial weight*
11/1	4	92	92
15/1		73	85
19/1		58	70
15/5	4	81	87
20/5		58	58
15/9	4	84	94
20/9		59	65
15/4	4	73	68
20/4		69	60
15/6	4	83	78
20/6		70	55
15/4	4	87	104
20/4		72	87
15/6	4	88	92
20/6		66	68
10/9	4	93	93
20/9		72	65
15/5	6	69	77
20/15		60	62
15/15	12	68	65
19/15		47	44

*Assuming that 60% of control kidney weight was tubular epithelium and that all weight loss was from loss of this epithelium. The 60% value is not critical· other arbitrary assumptions for this value show a better correlation between ^{86}Rb extraction than obtained from the raw data (*i.e.* from assuming 100% of kidney weight was involved in ^{86}Rb extraction).

tubules of the testis and 300 days in the tubules of the kidney.

It is generally agreed that the mechanism of radiation injury in the first five tissues is depletion of parenchymal cells and it is simplest to assume that the same mechanism underlies injury to the renal tubule epithelium and that the slow expression of injury reflects merely the slow turnover of this cell population.

Reconstitution of nephron. A question not answered by our study is whether the whole tubule, including both proximal and distal segments, can be regenerated from one cell whose progeny traverse the loop of Henle. That only a mean of 2.2 tubules composed the clusters in contact with the capsule after high doses, compared with an average of about four expected from the ratio of capsule-contacting tubules to glomeruli is not evidence of incomplete re-epithelialisation of tubules because the histological section provides only one of the two dimensions involved in tubule–capsule contact. No attempt was made to count tubules deeper in the cortex and medulla, but even if the proportionality of survival were the same in proximal and distal tubules there would be no guarantee that cells had traversed the loop of Henle to re-epithelialise the whole length of the tubule: the same picture could result from independent re-epithelialisation by surviving clonogens in various, approximately equal, subsets of the epithelial cell population along the length of the nephron. The answer to this question will probably require microdissection of kidneys at various intervals after various doses of radiation.

Clinical consequences of functional subunits. The debate regarding the pathogenesis of radiation nephropathy (and other slowly developing sequelae), which has been going on for at least 60 years, is not merely academic.

Tolerance doses. If, as our data suggest, a renal tubule, or a subsegment thereof, responded to radiation as an independent unit with the capacity to regenerate itself from a single cell, but without the capacity to repopulate adjacent nephrons, then it is clear that irreversible injury would occur after the relatively low doses that completely deplete a proportion of tubules of their epithelium (Withers et al, 1983). The influence on "tolerance" doses in radiotherapy of the structure and cellular content of the functional subunit is most easily contemplated in terms of an example. Suppose a kidney contained 10^{11} tubule epithelial cells. If there were 10^7 nephrons, each containing 10^4 cells, a radiation dose that reduced survival to 10^{-4} would permanently eliminate about 37% of the nephrons. If, on the other hand, there were only 10^4 nephrons, each containing 10^7 cells, then the dose required to eliminate 37% of the nephrons would be that required to reduce survival to 10^{-7}. In terms of multifractionated radiotherapy regimens that produced an equal effect per fraction, the tolerance dose under the second postulate would be 7/4 times (75%) greater than under the first. It is clear from the above example that tolerance of the kidney and, by analogy, other organs, would be governed by the number and radiosensitivity of the critical cells in the functional subunits, which is not the obvious conclusion when radiation nephropathy is considered to be a progressive vascular phenomenon.

Re-irradiation. The reluctance of most radiotherapists to re-irradiate the kidney, or other late-responding tissues, at any time after prior radiotherapy for cancer, because it is believed that vascular changes and, hence, "late" injuries are irreversible, needs re-evaluation. If parenchymal cell depletion were the pathobiological basis of late effects, the tolerance of a tissue to further irradiation could be assessed in terms of the extent of cellular depletion of functional subunits by prior irradiation and the time elapsing between two courses of radiation, during which surviving parenchymal clonogens could regenerate.

Acknowledgments

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APPENDIX

It is interesting to consider the implications of assuming that more than one surviving cell is necessary to regenerate a tubule. Let the probability of tubule regeneration = fraction of regenerating tubules = f. Assume first that cells are killed randomly and that two cells (anywhere in the tubule), rather than one, are necessary for tubule regeneration, that N = initial number of cells/tubule and S = average fraction of cells surviving a dose of radiation. Finally, let $p(k)$ = probability that k cells survive per tubule.

$$\begin{aligned} f &= p(\geqslant 2 \text{ cells survive/tubule}) \\ &= 1-(p(0)+p(1)). \end{aligned}$$

Therefore, from Poisson statistics:

$$\begin{aligned} 1-f &= e^{-NS}(1+NS) \\ &\simeq 1-1/2(NS)^2 \end{aligned}$$

if NS is much less than 1 (at low levels of tubule survival). The average number of tubule regenerating units is

$$\begin{aligned} &= -\ln(1-f) \\ &= -\ln(1-1/2[NS]^2) \\ &\simeq 1/2(NS)^2 \end{aligned}$$

The inverse of the slope of the survival curve is denoted by D_0, the dose to reduce average survival to e^{-1}. Therefore

$$\begin{aligned} &\frac{1}{D_0 \text{ (observed)}} \\ &= -\frac{d(\ln\,[\text{surviving tubule regenerating units/tubule}])}{d\,(\text{dose})} \\ &= -2\frac{d(\ln\,(NS))}{d(\text{dose})} \\ &= \frac{2}{D_0\,(\text{cells})} \end{aligned}$$

i.e. D_0 (cells) = $2D_0$ (observed).

Similar, but more complex calculations indicate that the divergence between D_0 (cells) and D_0 (observed) would continue with increasing number of cells required for tubule survival.

Alternatively, assume that the N cells are organised into M associated networks, each consisting of x cells ($N = Mx$) and that all cells in a network must survive for that network to regenerate a tubule. Then p (network survival) = S^x, and average number of surviving networks = MS^x. Therefore, the fraction of regenerating tubules

$$\begin{aligned} f &= p(\geqslant 1 \text{ network survives}) \\ &= 1-p(0 \text{ networks survive}) \\ &= 1-e^{-MS}. \end{aligned}$$

Therefore, the number of survivors/structure = $-\ln(1-f) = MS^x$, and

$$\begin{aligned} &\frac{1}{D_0 \text{ (observed)}} \\ &= -\frac{d(\ln\,(\text{number of survivors/tubule}))}{d(\text{dose})} \\ &= x\frac{d\,(\ln\,(NS))}{d(\text{dose})} \\ &= \frac{x}{D_0(\text{cells})} \end{aligned}$$

i.e. D_0 (cells) = xD_0 (observed).

Since mammalian cells are consistently characterised by D_0 values of about 1 to 1.8 Gy, then, unless renal tubule cells are unexpectedly more radioresistant than other mammalian cells, the observation of a D_0 value of about 1.5 Gy for tubule survival establishes that tubules were regenerated from single surviving cells.

Book reviews

Radiology of Adverse Reactions to Drugs and Toxic Hazards. By George Ansell, pp. ix + 389, 1985 (Chapman and Hall, London), £30.00.
ISBN 0-412-22140-3

The author's interest and vast experience in the topic of reactions to drugs and toxic substances is well known. He has now produced a scholarly work on the radiology of these reactions. This is the second edition of the book first published in 1974 under the title *Radiology in Clinical Toxicology*. There can hardly be a reaction that is not covered by this book. Approximately 1200 references are given so that the work is a valuable source-book of information.

The descriptions are given under five sections: the chest, gastrointestinal tract, renal tract, skeletal system and soft tissues and, finally, the skull and central nervous system. The script is concise, easily read and interesting. The various reactions are lavishly illustrated, there being over 150 illustrations. As the author points out, many of the appearances produced are similar to more common conditions so that the awareness of the possibility of a toxic reaction is an important factor in reaching a diagnosis. This work will assist greatly in this respect.

Dr Ansell is to be congratulated on producing an excellent book which will establish itself as a standard reference work. It is of interest to radiologists and all clinicians. It should be obtained by all radiological departmental libraries and by hospital and medical school libraries.

I. H. GRAVELLE

Carbon-14 in the Environment. NCRP Report No. 81. pp. vi + 108, 1985 (NCRP, Bethesda), $12.00.
ISBN 0-913392-73-1

This publication is the report of a task-group set up by the Council's scientific committee 38 (Waste Disposal).

Carbon 14, with a half-life of 5.7×10^3 years, is a natural component of our environment, originating from cosmic-ray interactions in the atmosphere. This natural source has been augmented by nuclear weapons testing and, to a lesser extent, by emissions from nuclear power reactors.

The report summarises the available information on ^{14}C in terms of its physical properties, sources, distribution in the environment and biology. It also discusses methods of sampling, analysis, dosimetry and waste disposal. An attempt is also made to evaluate its importance as a potential source of local and worldwide radiation exposure and, using compartmental-analysis models, whole-body-equivalent doses are estimated up to the year 2000.

The information is allocated to eight sections and the book is rounded off with a short glossary of technical terms, a comprehensive reference list of over 250 publications and an index.

Following a short introduction/summary (Section 1), Section 2 deals with the radiochemical properties of ^{14}C and Section 3 with the principal sources, natural and man-made. Section 4 considers ^{14}C in the biosphere, its distribution in the atmosphere, on land and in the sea, and the various interchange pathways and fluxes between them. Section 5 summarises the techniques of sampling and the methods of analysis. The behaviour of ^{14}C in biological systems is investigated in Section 6 and data given for its retention and excretion in various organisms and its incorporation into molecules of biological importance. Section 7 leads into compartmental-analysis modelling of ^{14}C in the environment, its exchange and equilibrium and, after a short excursion into dosimetry, estimations and prognostications regarding the dose to man from the three major environmental sources are made (and shown graphically) up to the year 2000. The last section (8) deals with the management of ^{14}C waste, the amount of which is minimal compared with that from many other radioactive sources.

The immediate human exposure is internal, through inhalation and ingestion, and since the metabolism of ^{14}C is similar to that of ordinary carbon, a fraction of that taken in is incorporated into body tissues. However, the report concludes that the radiation dose to human beings from this source will be insignificant for the foreseeable future. The contribution from fall-out is expected to decrease with time, whilst that from nuclear power reactors will increase but remain at a level two orders of magnitude less than that from naturally produced ^{14}C, this latter being an absorbed tissue dose-rate in man of 1.25 mrad per year (*i.e.*, about 1% of the average annual total-body natural background absorbed dose-rate of 100 mrad).

Here we have another concise and well prepared document from NCRP, ideal for keeping the busy scientist up to date.

JOHN R. K. SAVAGE

1986, *The British Journal of Radiology*, 59, 597–602

JUNE 1986 •

Protection against ionising radiation and synergism with thiols by zinc aspartate

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ABSTRACT

Pre-treatment with zinc aspartate protected mice against the lethal effects of radiation and raised the LD_{50} from 8 Gy to 12.2 Gy. Zinc chloride and zinc sulphate were clearly less active. The radioprotective effect of zinc aspartate was equivalent to cysteamine and slightly inferior to S,2-aminoethylisothiourea (AET). Zinc aspartate displayed a similar therapeutic index to the thiols but could be applied at an earlier time before irradiation. Synergistic effects occurred with the combined administration of zinc aspartate and thiols. By giving zinc aspartate with cysteamine, the LD_{50} was increased to 13.25 Gy and, by combining it in the optimal protocol with AET, to 17.3 Gy. The radioprotection by zinc and its synergism with thiols is explained by the stabilisation of thiols through the formation of zinc complexes.

The practical importance of radioprotective compounds is undisputed. Chemical protection of mammals against ionising radiation (Doherty, 1960) was initiated by the discovery that sulphydryl-containing agents (thiols) such as cysteine (Patt et al, 1949), cysteamine (2-mercaptoethylamine) (Bacq et al, 1953), glutathione (Chapman & Cronkite, 1950) and S,2-aminoethylisothiourea (AET) (Doherty & Burnett, 1955) were active. Since with these mercapto-alkylamines and aminoalkylisothioureas near-toxic conditions had to be maintained to obtain maximal effects, it was stated that "since it is unlikely that simple substances will possess the requisite properties to saturate every radiation sensitive system, the promise for increasing further mammalian tolerance to radiation probably lies in a combination of effective compounds" (Doherty, 1960).

A considerable increase in the resistance to ionising radiation was brought about by the introduction of phosphorothioates as radioprotective drugs with S-2-(3-aminopropylamino)ethylphosphorothioic acid (WR 2721) as the most promising agent (Yuhas & Storer, 1969; Sweeney, 1979; Davidson et al, 1980). However, the use of WR 2721 as a radioprotector in man is compromised by toxic effects which occur at much lower doses than those assumed to be necessary for significant radioprotection in mammals (Cairnie, 1983).

The observation (Tobey et al, 1982) that the resistance of cultured hamster cells to melphalan, an alkylating agent displaying "radiomimetic" properties (Elson, 1963), could be enhanced by *in-vitro* pre-treatment with zinc chloride prompted us to study whether zinc salts would also be active alone or in combination with conventional radiation protectors to modify the effects of whole-body ionising irradiation.

MATERIALS AND METHODS

Mice and irradiation

The experiments were carried out with female C3H mice (Gl.Bomholtgard, Ry,Denmark), weighing 20–22 g and fed Nafag pellets and tap water *ad libitum*. Groups of mice were irradiated in a perforated plexiglass chamber from a cobalt-60 source (Gammatron) at a dose rate of 0.3 Gy min^{-1}. The target distance was 80 cm. The mice were injected prior to irradiation at the times indicated in Tables I–III. Survival of the mice was followed up to Day 30 after radiation and is shown in Tables I–III. The median survival time in the controls was dose-dependent and with 9 Gy was 12.3 days (range 10–17 days), with 10 Gy was 11.2 days (range 9–15 days), with 11 Gy was 9.5 days (range 8–12 days), with 12 Gy was 8.7 days (range 7–11 days), with 13 Gy was 8.3 days (range 6–11 days) and with 14 Gy was 6.2 days (range 4–8 days). The LD_{50} in the controls was 8 Gy.

Drugs

Zinc was used as either zinc aspartate (zinc-*bis*-(DL-hydrogenaspartate)), zinc chloride ($ZnCl_2$) or zinc sulphate ($ZnSO_4 . 7H_2O$); AET was used as S,2-aminoethylthiouronium bromide hydrobromide. The agents were dissolved in distilled water and injected in 0.1 ml/10 g body weight by the intraperitoneal route. For cysteine (L-cysteine HCl), cysteamine (cysteamine HCl) and glutathione (GSH), the pH was adjusted to 7.0 by adding 2N NaOH. The controls received only distilled water (0.1 ml/10 g body weight) 10 min prior to irradiation. The LD_{50} of the zinc salts was 55 mg/kg (zinc aspartate), 24 mg/kg (zinc chloride) and 47 mg/kg (zinc sulphate). The LD_{50} of cysteamine was 375 mg/kg and of AET, 415 mg/kg.

RESULTS

We tested the effect of pre-treatment with zinc aspartate, zinc chloride and zinc sulphate on the

TABLE I

SURVIVAL (30 DAYS) OF MICE IRRADIATED WITH 9–13 GY AND PRE-TREATED WITH ZINC ASPARTATE

Zinc aspartate dose (mg/kg)	Applied at (min before irradi-ation)	Survival* after (Gy) 9		10		11		12		13	
		No.	%	No.	%	No.	%	No.	%	No.	%
0 (controls)		1/59	2	0/73	0	0/60	0				
10	10	1/10	10								
20	10	26/39	67	13/45	29	0/20	0				
20	30	6/10	60	1/10	0						
20	120	5/10	50	0/10	0						
30	10	43/49	88	43/58	74†	3/30	10	1/30	3	0/20	0
30	30	8/10	80	21/30	70	24/40	60†	17/30	57†	5/30	17
30	120	9/10	90†	8/20	40	16/30	53	7/20	35	4/29	14
40	10	17/29	59	16/29	55	1/40	3	5/30	17	1/19	5
40	30	9/20	45	7/10	70	5/10	50	3/10	30	7/29	24†
40	120	5/10	50	5/10	50	1/10	10	0/10	0	1/19	5

*No. of surviving mice/total No. of mice.
†Points used for the construction of Fig 1.

survival of mice subjected to lethal doses of radiation from a cobalt-60 γ-ray source. The results (Table I) show that survival was markedly enhanced with zinc aspartate. With 30 mg/kg zinc aspartate applied at different times before irradiation with the lethal dose of 9 Gy, a consistent survival of 80–90% was observed. With the doses of 20, 30 and 40 mg/kg of zinc aspartate, the time of application, whether 10, 30 or 120 min prior to the irradiation with 9 Gy, did not influence the results significantly. With 11 Gy and 12 Gy, an interval of 30 min led to the highest survival rates. With zinc chloride (10–20 mg/kg), the survival rate after 10 Gy was about three- to fourfold less than with optimal doses of zinc aspartate. Zinc sulphate

TABLE II

SURVIVAL (30 DAYS) OF IRRADIATED MICE AFTER PRE-TREATMENT WITH THIOLS

Therapy/ dose (mg/kg)	Applied at (min before irradiation)	Survival* after (Gy) 9	10	11	12	13	14
Controls (0)		0/10	0/10	0/10			
Cysteamine							
150	10	10/10	9/10	0/10			
225	10		10/10†	8/10†	6/10†	1/10†	0/10
225	30			6/10	1/10		
225	120			0/10			
Cysteine							
600	10	7/10	3/10				
900	10	10/10†	4/10	0/10			
1200	10		9/10†	2/10†	1/10†		
1200	30			0/10			
l-Glutathione							
1000	10	3/10					
2000	10	2/10					
AET							
125	10			0/10		0/10	
250	10			10/10†	9/10†	2/10†	0/10
250	30			10/10			
250	120			0/10			

*No. of surviving mice/total No of mice.
†Points used for the construction of Fig. 1.

TABLE III

SURVIVAL (30 DAYS) OF MICE IRRADIATED WITH 12–18 GY AND PRE-TREATED WITH ZINC ASPARTATE COMBINED WITH AET OR CYSTEAMINE

Zinc aspartate		AET/cysteamine		Survival* after (Gy)						
Dose (mg/kg)	Applied at (min before irradiation)	Dose (mg/kg)	Applied at (min before irradiation)	12	13	14	15	16	17	18
		AET								
10	30	125	10			8/15	1/10	0/10		
10	30	250	10			10/15	6/10	1/10		
20	30	62.5	10			5/15	4/10	0/10		
20	30	125	10		10/10†	19/20†	0/10	1/10	0/10	
20	30	250	10		7/10	15/20	8/10	5/10	2/10	0/10
30	30	62.5	10			14/15	9/10†	3/10		
30	30	125	10		8/10	15/20	7/10	8/10	6/10†	3/10†
30	30	250	10		0/10	2/5				
30	120	250	10		5/8	7/15	5/10	9/10†	1/10	3/10†
30	10	250	10		5/9	2/5				
20	10	125	10	7/10		2/10				
20	30	125	30			0/5				
		Cysteamine								
20	30	225	10		4/10	0/10				
30	30	225	10	9/9†	12/18†	0/10				
30	120	225	10		2/20	0/10				
40	120	225	10		6/10					

*No. of surviving mice/total No. of mice.
†Points used for the construction of Fig. 1.

(15–30 mg/kg) was essentially ineffective against 11 Gy while zinc aspartate applied 30 min before irradiation afforded a survival rate of up to 50–60%. Aspartate may provide zinc in an advantageous form, perhaps due to the high affinity of asparagine to the intracellular space (McMenamy et al, 1960; Soupart, 1962) and also to its capacity to form stable chelates which favour the transport of metals and trace elements into cells. Both Cu-DL-aspartate (10–30 mg/kg) and Na-DL-aspartate (20–1000 mg/kg) tested at 10 min before irradiation against 9 Gy were ineffective.

The comparison of the protective effects of zinc aspartate with those afforded by conventional radioprotective agents, *i.e.* sulphydryl groups containing aminoalkylthiols (Table II, Fig. 1), showed clearly that glutathione and cysteine were less effective. With 225 mg/kg cysteamine, applied 10 min before irradiation, the LD_{50} after radiation could be raised from the

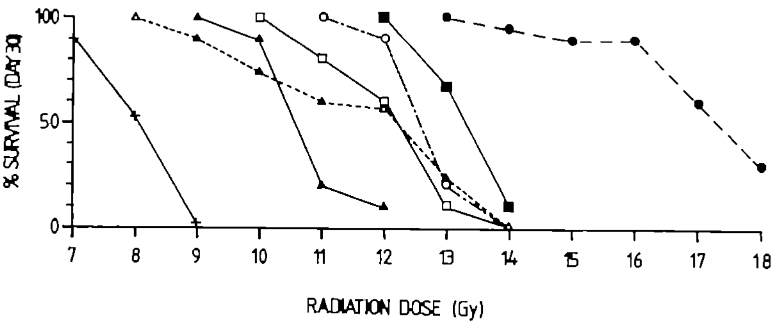

FIG. 1.

Survival of irradiated mice after treatment with optimal protocols of zinc aspartate (△), cysteine (▲), cysteamine (□), AET (○), zinc aspartate + cysteamine (■) and zinc aspartate + AET (●) compared with controls (+). The groups used for each point of the survival curves in the dose range of 9 Gy to 18 Gy with the respective protocols are indicated in the Tables I–III. In the 7–8 Gy dose range, the survival rate of the controls was 9/10 (90%) with 7 Gy and 15/28 (53%) with 8 Gy. Against 8 Gy, 10 out of 10 mice survived after therapy with either 20 mg/kg or 30 mg/kg zinc aspartate administered 30 min or 120 min before irradiation.

control value of 8 Gy, as with zinc aspartate, to 12.2 Gy. The protection factor, *i.e.* the quotient of the radiation LD_{50} in the presence and in the absence of the protector, was 1.52, although the slope of the radiation dose–response curve was less steep with zinc aspartate than with cysteamine. With AET, the LD_{50} was, with 12.75 Gy, slightly higher and the protection factor, 1.59.

A marked further increase in radiation resistance was obtained by combining zinc aspartate with either cysteamine or AET (Table III, Fig. 1). At 12 Gy, the best individual survival rates with zinc aspartate or with cysteamine, of approximately 60%, were elevated to 100% by giving both agents. By this means it was also possible to improve the marginal survival obtained with the individual agents at 13 Gy to 67% and 100%, respectively, by combining zinc aspartate with cysteamine or with AET. With the combined regimen of cysteamine and zinc aspartate, the protection factor was 1.66.

The best results were seen when zinc aspartate and AET were combined. With the optimal protocols, the survival rates against up to 16 Gy were 90% to 100% (Table III, Fig. 1). The increase in the LD_{50} from 8 Gy to 17.3 Gy corresponds to a protection factor of 2.16. Low (62.5 mg/kg) and medium (125 mg/kg) doses of AET markedly enhanced the activity of a high dose of zinc aspartate (30 mg/kg). Conversely, low or medium doses of zinc aspartate (10 mg/kg and 20 mg/kg) enhanced the effect of the high AET dose (250 mg/kg). Combining the high doses yielded lower survival rates due to the loss of mice from toxicity within the first 4 days after administration of the drugs. This toxicity could be obviated to some extent by applying zinc aspartate 120 min before irradiation, but the somewhat erratic persisting toxicity precluded a strictly dose-dependent survival pattern with the high-dose protocol. Otherwise, zinc aspartate was applied at 30 min and AET at 10 min before irradiation. If both agents were not applied in this sequence but simultaneously at either 30 min or 10 min before irradiation, inferior results were seen (Table III).

DISCUSSION

The mechanism by which the mercaptoalkylamines and AET protect against ionising radiation has been linked to an interaction with radiation-induced free (H·,OH·) and peroxy (HO_2·) radicals (Eldjarn & Pihl, 1957; Doherty, 1960). It was suggested that mixed disulphide formation of the protective thiols with essential thiols of the target molecule shields the latter by providing a non-lethal target for radiation-induced radicals (Eldjarn & Pihl, 1957). Moreover, the formation of the disulphide bond generates free electrons, which leads to the repair of an electron deficiency elsewhere in the molecule and, thereby, to the regeneration of essential thiols. The radioprotective effect of zinc aspartate can be explained by the formation of zinc complexes with low- or high-molecular-weight thiols present in cells. The formation constants (log K_1) of Zn^{2+} complexes with 2-mercaptoethylamine (9.90), cysteine (9.86) and glutathione (8.30) indicate the high affinity of Zn^{2+} for thiols (Li & Manning, 1955). The activity of thiol groups in general and all molecular processes that are induced in the cell by radiation and involve thiols are, therefore, influenced by Zn^{2+}. This also includes the radioprotective action of AET, which, after transguanylation, provides a free thiol group. One can, thus, assume that the binding of Zn^{2+} to thiol groups protects them against the radical-forming and oxidising action of radiation, perhaps even with a qualitative preference for exposed and essential thiol groups. This stabilisation of the thiol content in cells by zinc would also apply to exogenous thiols, thus explaining the observed radioprotective synergism of zinc aspartate and thiols.

The possible protective rôle of zinc for thiols in free-radical-induced tissue damage has already been proposed (Willson, 1976, 1977a, b) and supported by some *in-vitro* studies (Bahnemann et al, 1978; Searle & Tomasi, 1982). In particular, it was reasoned that the formation of damaging superoxide radicals with thiol–iron complexes may be inhibited by competitive binding of zinc to critical thiol groups. Accordingly, it was suggested that an increase in the zinc–iron ratio in cells may confer protection from iron-catalysed free-radical-induced damage. In line with the suggested possibility of an increased radiation-induced tissue damage associated with low zinc levels (Willson, 1976) was the observation that a decrease in serum zinc after administration of the drug bleomycin correlated well with the increased sensitivity of mouse skin to radiation damage (Leith et al, 1975).

In addition to its possible rôle in protecting thiols from oxidation, it must also be considered that zinc is known to be an important component of over 100 enzymes, including several involved in DNA synthesis and repair. It is also a component of superoxide dismutase, claimed to protect against free-radical-induced injury. However, 100 mg/kg of this enzyme (Peroxinorm, Grünenthal GmbH) applied by the intraperitoneal route 10 min before irradiation failed, in preliminary experiments, to protect mice against lethal irradiation.

With the combined administration of zinc aspartate and AET, doses of one agent with little or no effect when used alone enhance the response to effective doses of the other. This would be consistent with synergism in the action of zinc and thiols. The fact that zinc aspartate and the combined protocol, like thiols, are ineffective when administered after the irradiation agrees, too, with the proposed radioprotective mechanism. While the enhancement of the radioprotection afforded by thiols by the administration of zinc explains the superior radioprotective effect of combination therapy, it must also be asked whether the toxic manifestations display synergism due to an identical stabilisation of thiols by zinc. Indeed, high doses of zinc aspartate (30 mg/kg) or AET (250 mg/kg) are well tolerated when given alone, but poorly tolerated when administered in combination. As to the nature of the toxicity caused by zinc or the combined treatment with zinc and thiols, pertinent studies are needed. Lethal doses of AET or cysteamine are thought to cause death by cardiorespiratory failure (Di Stefano et al, 1956). Even low doses of AET are accompanied by intolerable side-effects in man (Condit et al, 1958).

It might be rewarding to determine the potentiating action of zinc aspartate or other organic zinc salts for other thiols, such as the more effective radioprotective agents (including WR 2721) uncovered in the very extensive testing programme of the US Army Research and Development Command (Sweeney, 1979).

The administration of thiols to prevent radiation injury has been limited by the high and near-toxic doses required. With zinc aspartate, equieffective protective doses/body weight are about eight times lower than with cysteamine or AET. Although in mice the relation between the LD_{50} and the optimal protective dosage as identified in our experiments was similar, namely 1.8 with zinc aspartate and 1.7 with cysteamine or AET, an advantage of zinc salts may be their good tolerance in humans (Tschumi & Floersheim, 1981). Zinc aspartate retains its activity longer than cysteamine or AET. For instance, zinc aspartate administered 120 min before 11 Gy allowed 53% of the mice to survive while no survival was seen with cysteamine or AET applied at this interval.

Since the therapy with zinc and AET afforded survival against radiation doses of 14 Gy and more, it can be assumed that the combined protocol protects not only against the relatively delayed death due to bone marrow failure (haemopoietic death) but also against the gastrointestinal death (gut damage) which is fatal within a shorter range of time (approximately 5–8 days). It must also be mentioned that, although we used overall survival at 30 days to evaluate the radioprotectors, survival of mice which succumbed to radiation in spite of radioprotective therapy was always prolonged when compared with the respective untreated control groups.

In addition to the prevention of radiation injury, radioprotective agents may be used in radiation therapy for cancer and other diseases. It remains to be seen whether the radiation resistance of the animals is increased with zinc aspartate to a different extent from the resistance of the cancer cells or of other tissues which may be the target for radiation therapy. Further, it will be interesting to assess whether the synergism between zinc aspartate and thiols applies also to other potential uses of sulphydryl compounds, including conditions where active oxygen, organic peroxides and radicals are supposed to be involved in the pathogenetic mechanism (Willson, 1977b; Dormandy, 1983; Anonymous, 1985), such as inflammatory tissue and joint injury, carcinogenesis, the aging process and hepatotoxic damage. In acute alcoholic liver injury, where thiols are known to reduce the damage (MacDonald et al, 1977), a protective activity by zinc aspartate has been demonstrated (Floersheim, 1985).

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Technical note

A technique for velocity imaging using magnetic resonance imaging

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Magnetic resonance imaging (MRI) is becoming well established as a technique which both shows anatomy and allows tissue characterisation. A further development of the technique allows the imaging of regular movement such as blood flow and cardiac wall motion. In particular, much effort has been put into developing techniques for imaging flowing blood and deducing such parameters as velocity and acceleration.

Early work by Singer (1959) described a technique of blood flow velocity measurement using a "time-of-flight" method. Velocity images have been obtained by this method using a modified version of a spin-echo pulse sequence (Feinberg et al, 1984). Normally, a slice is excited using a selective 90° radio-frequency (RF) pulse and an echo is produced at a later time by applying a selective 180° pulse to the same slice. If moving hydrogen nuclei have, in the meantime, moved out of the slice, no signal will be returned from them, resulting in a reduction in signal intensity from blood vessels in the image. This is the spin washout effect. If, however, the 180° RF pulse is applied to a slice downstream, an echo signal will be returned from excited nuclei having a velocity such that they coincide with the second slice selection. In this way, a series of images can be obtained, each corresponding to a certain range of velocities.

The standard spin-echo technique can also be exploited to produce flow-dependent signals in vessels (Axel, 1984; Bradley et al, 1984; Waluch & Bradley, 1984). The effect, known as paradoxical enhancement, results in vessels appearing to have a much higher intensity than the surrounding tissue. This effect becomes particularly noticeable for shorter repetition times since freshly saturated nuclei moving into the slice will give a stronger signal relative to the surrounding stationary tissue, which is only partially saturated.

In a multi-echo sequence a phenomenon known as even-echo rephasing is also present (Waluch & Bradley, 1984). The magnetic field gradient (subsequently referred to as the gradient) used for slice selection and the gradient used for readout are applied twice in a spin-echo sequence. The first time they are applied, nuclei dephase along the direction of the gradient; the second time, they are applied with opposite polarity and nuclei move back into phase along that direction. If the nuclei are stationary then they will move back exactly into phase with one another; however, if nuclei are moving along a gradient direction they will have a phase shift at the first echo, having only partially rephased. This phase shift will be linearly dependent on their velocity. All nuclei having the same velocity will have the same phase shift on odd echoes but will have zero phase shift on even echoes, the effect of the gradients having been reversed provided the velocity is constant. Thus, flow can be identified by comparing first and second echo images. On the first echo, flowing blood will appear to have a reduced signal while, on the second echo, the signal will be of higher intensity. We are, of course, neglecting dephasing effects caused by spin-spin relaxation.

Since the non-zero phase shift on the first echo is linearly dependent on velocity, it can be used to measure velocity directly (Bryant et al, 1984; Moran & Moran, 1984; Redpath et al, 1984; Van Dijk, 1984; Moran et al, 1985; Wedeen et al, 1985). In most MRI systems the signal is collected from two channels in quadrature, yielding a real and an imaginary data set. These are usually combined to calculate a modulus image used for diagnosis. These two data sets can, however, be used separately to produce a real or an imaginary image, or can be combined to calculate a phase image. All three of these contain phase information which is normally discarded in the calculation of the modulus image and it is this information which provides a way of imaging velocity.

Although real and imaginary images have been used to demonstrate imaging of velocity, they also contain spin-density information (Moran et al, 1985). The phase image is easiest to interpret and quantify since it contains only motion information and represents a direct linear map of a single velocity component. In order to quantify the velocity measurements accurately, standard spin-echo and field-echo sequences have been modified by adding extra gradient pulses in the direction of required velocity measurement.

To date, this has been done in two ways (Moran et al, 1985); either two identical gradient pulses separated by a 180° RF pulse are inserted, or a bipolar pulse consisting of two successive gradient pulses equal in magnitude and duration but of opposite sign is inserted into the pulse sequence between the 90° RF pulse and the readout gradient. The first of these gradient pulses dephases the nuclei in the applied direction and the second pulse rephases them. Stationary nuclei are all brought back into phase, whereas for nuclei moving along the gradient the rephasing is not complete, leaving them with a phase shift proportional to velocity.

The accuracy of the technique is dependent on the two gradient pulses having exactly the same duration and magnitude over the imaging volume and on the uniformity of the RF, gradient and static fields. A non-uniform field will introduce a spatially dependent phase shift over the image (McVeigh et al, 1985; Norris, 1985b). A technique has been developed (Redpath et al, 1984) to overcome these difficulties by varying the size of the flow-encoding pulses for a number of data acquisitions and applying a 3D Fourier transform technique to the whole set of data. The resultant set of images will be coded in intensity, each corresponding to a certain velocity range, and may be used to reconstruct a simple velocity-coded image. A further limitation of the techniques is that velocities corresponding to a phase shift of greater than +180° or less than −180° will lead to an ambiguity of velocity measurement. This can be avoided by adjusting the magnitude of the gradient so that the resultant phase shifts lie within the range of ±180°. This paper presents a technique which uses the calculated phase image as a direct measurement of velocity. The problem of field non-uniformity is avoided by using two separate pulse sequences and subtracting the resultant phase images.

METHOD

The technique has been integrated into the standard spin-warp imaging sequence (Edelstein et al, 1980) used on an M&D 0.08 T resistive MRI system (Smith et al, 1984). The slice selection gradients, which are effectively of bipolar form, were initially used to provide the phase encoding for velocity components perpendicular to the imaging slice (Fig. 1). In order to avoid the appearance of phase shifts due to the spatial non-uniformities of the fields, two pulse sequences were used to produce two phase images which were subtracted to produce the final velocity image. The two pulse sequences were identical except that the timing of the rephasing gradient was later in one than in the other. Phase errors due to the time-independent inhomogeneities in the main field and the RF field would be the same in each case and would, thus, cancel in the final subtracted image. The only remaining phase differences are due to motion, such that for a given velocity component, v, in the direction of the applied slice selection gradient, G, the phase difference is:

$$\phi_{\text{diff}} = -\gamma G v t_w t_{\text{diff}}$$

where t_w is the duration of the rephasing pulse, t_{diff} is the difference in pulse separation for the two pulse sequences, and γ is the gyromagnetic ratio for protons (Fig. 1).

All the computer processing is performed within the acquisition program so that the subtracted phase images are displayed 8 s after acquisition. An ungated velocity image can be obtained in 64 s using a repetition time (TR) of 250 ms. For *in-vivo* imaging, however, the pulse sequences are gated (Been et al, 1985) in order to look at an instantaneous velocity, and consequently the imaging time is dependent on the heart rate. Typically, one section will take about 4 min. The two pulse sequences are interlaced so as to reduce the effects of gross patient movement between scans. The magnitude of the flow pulse gradient, G, is $1.25\ \text{mT m}^{-1}$. For the studies described here, the flow pulse timing was such that $t_{\text{diff}} = 2$ ms and $t_w = 2.4$ ms. The velocity sensitivity can be increased simply by increasing t_{diff}.

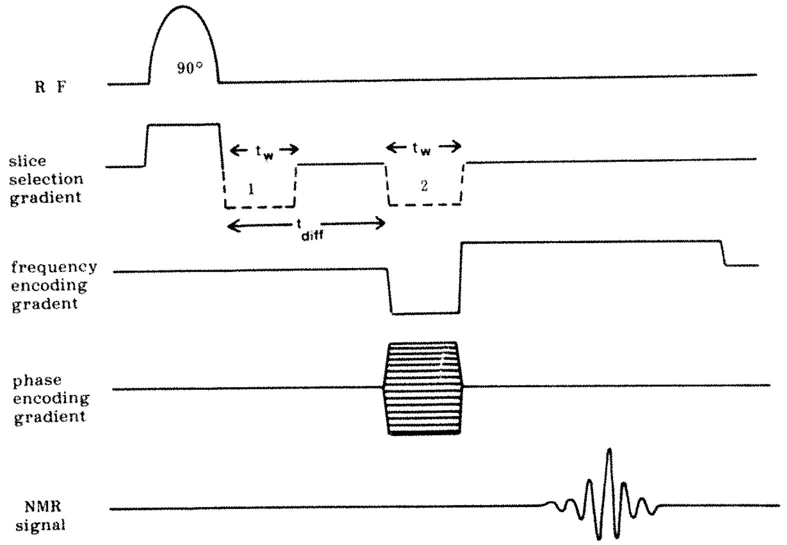

FIG. 1.

A simple adaption of the Aberdeen spin-warp pulse sequence for imaging of velocity through the slice by varying the position of the rephasing gradient (broken line) between positions 1 and 2. Two corresponding phase images are produced and then subtracted to produce the velocity-coded image.

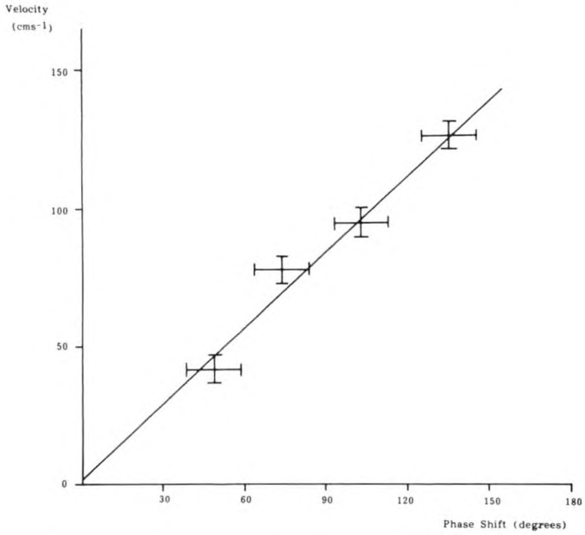

FIG. 2.

Velocity calibration of the flow measurement technique using the pulse sequence in Fig. 1.

Velocity measurements have been calibrated using a simple flow phantom consisting of a 1 cm-inside diameter polythene tube surrounded by a bath of 2.5 mM solution of copper sulphate. The same solution of copper sulphate was pumped through the tube at various known constant rates. The mean flow velocity for the tube was calculated and calibrated against the mean phase shift found within the tube. A number of normal volunteers have been imaged in the neck, thorax and abdomen using the interlaced gated sequence. An initial comparison with continuous wave Doppler ultrasound at 2.5 MHz has been carried out in the abdominal aorta using a Hewlett Packard 77020 Doppler imaging system. Using MRI, a number of delays were used from the electrocardiogram R-wave in order to plot the velocity in the abdominal aorta over the systolic period of the heart cycle. The sample volume for this measurement was taken at the centre of the aortic diameter.

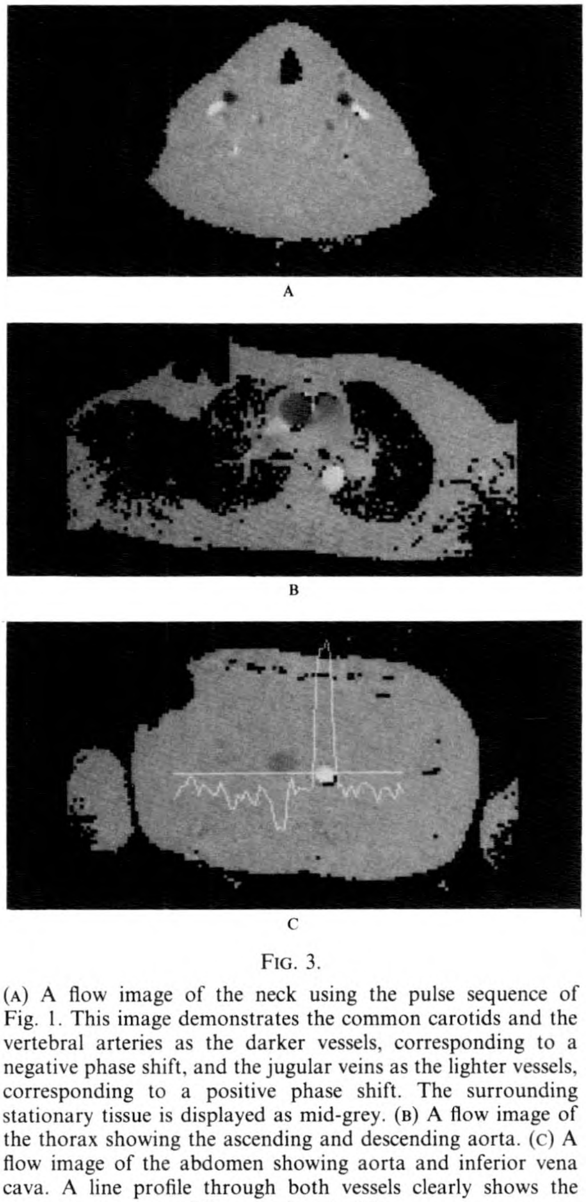

FIG. 3.

(A) A flow image of the neck using the pulse sequence of Fig. 1. This image demonstrates the common carotids and the vertebral arteries as the darker vessels, corresponding to a negative phase shift, and the jugular veins as the lighter vessels, corresponding to a positive phase shift. The surrounding stationary tissue is displayed as mid-grey. (B) A flow image of the thorax showing the ascending and descending aorta. (C) A flow image of the abdomen showing aorta and inferior vena cava. A line profile through both vessels clearly shows the differences in velocities.

RESULTS

The calibration of the velocity measurement shows a good linear relationship between velocity and phase shift (Fig. 2). Three examples of the volunteer studies are shown in Fig. 3. These images display zero phase shift as mid-grey, positive phase shift of 180° as white and negative phase shift of 180° as black. Where the values in the modulus image are below a certain threshold the phase values are not calculated.

Figure 4 shows the velocity measurements taken in the abdominal aorta compared with those taken from continuous-wave Doppler ultrasound measurements. There is a good agreement in profile shape and timing, although the velocities appear to be lower in the case of the Doppler measurements.

DISCUSSION

It has been shown that velocity measurements are possible on the low field imaging system at Edinburgh with changes only to the pulse sequence and software and without any improvements required on the field homogeneity.

This technique, using phase as a direct measurement of velocity, has advantages over the other techniques

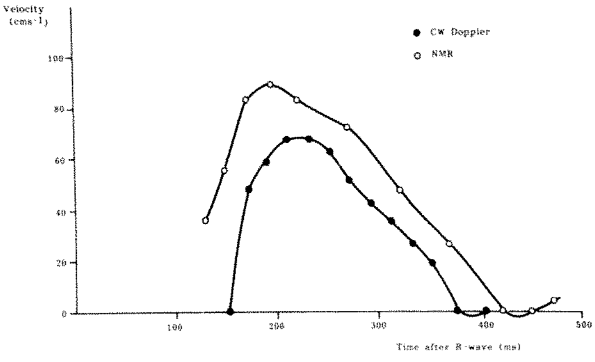

FIG. 4.

A velocity flow profile of the systolic period of the heart cycle for the abdominal aorta comparing the results from 11 flow images as shown in Fig. 3c, with results from Doppler ultrasound measurements.

mentioned in the introduction due to its relative simplicity in interpretation, processing and display. The time-of-flight method is restricted to imaging of one particular velocity range per image. Paradoxical enhancement and even echo rephasing are not quantitative measures of flow and can only be used to identify whether flow is present. The 3D Fourier transform method requires many flow encoding stages, whereas the technique described here requires only two sections to produce the final velocity image.

Initially, high flow velocities are being examined since they occur in the larger, better defined vessels. Lower velocities of the order of 1 cm s^{-1} have been imaged by the technique simply by extending the time t_{diff}. However, if this becomes too large then inhomogeneities in the field lead to loss of signal from the imaging slice, so it would be necessary instead to increase the magnitude of the flow gradient.

While peak velocity in the abdominal aorta can easily be imaged, the peak velocity in the ascending aorta is rather more difficult to image due to loss of signal around high velocity gradients over the vessel cross-section (Moran & Moran, 1984; Moran et al, 1985; Wedeen et al, 1985). These large velocity gradients result in a large range of velocities and, hence, a large range of phase shifts being present in the same pixel volume. This phase dispersion causes the signal from the nuclei in the same pixel volume to cancel, resulting in loss of signal, and is often seen as a dark line along the inner surface of the vessel. This effect can be seen even in standard pulse sequences, as the slice selection and signal readout gradients induce accidental phase shifts for nuclei moving in their direction. Of particular importance is the case of mitral-valve stenosis where high-velocity jets are present.

Methods have been suggested to overcome the phase dispersion which causes this loss of signal (Le Roux & Floch, 1985; Pattany & Naylor, 1985). It is proposed to use an adaption of the compensating bipolar pulse technique suggested by Le Roux and Floch, modifying it for use with the basic spin-warp pulse sequence. The compensating bipolar pulse is of opposite polarity to that already in the sequence, so that the dephasing effect is reversed. Figure 5 shows the suggested pulse sequence for use in further work, incorporating compensating bipolar pulses into the technique in all three directions. At present, this is not possible to do due to hardware limitations, although it is hoped to implement it in the near future.

It has already been shown (Norris, 1985a) that double bipolar pulses can be used to image acceleration. The greater the separation between the bipolar pulses, the greater the phase shift for a given acceleration. Thus, phase shifts due to acceleration can be minimised by merging the two middle pulses of the double bipolar flow pulse into one. The velocity measurement is achieved by varying the position in time

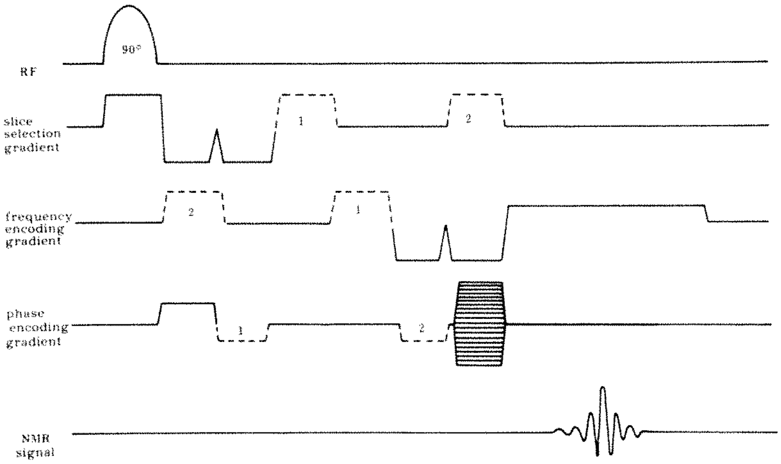

FIG. 5.

A further adaption of the flow pulse sequence of Fig. 1 for measurement of blood flow velocity in all three orthogonal directions. The gradient pulse sequences in the slice selection and frequency encoding directions have two bipolar pulses to compensate for the phase dispersion found in the normal imaging sequence.

of the broken line pulses in Fig. 5 between positions 1 and 2. Using the previous notation, the expression for phase shift is given by:

$$\phi_{\text{diff}} = \gamma G v t_w t_{\text{diff}} + \gamma G a t_w (7 t_w t_{\text{diff}} + t_{\text{diff}}^2)$$

where a is the constant acceleration.

Thus, for conditions where maximum acceleration occurs *in vivo* (200 cm s^{-2}) this would produce at most a 10% error in velocity measurement, given that typical velocities at this point are around 50 cm s^{-1}.

It is proposed to extend the technique to the measurement of flow in all directions in all phases and to pursue further volunteer studies and initial clinical trials. The technique will be compared directly with results from Doppler ultrasound measurements where possible.

ACKNOWLEDGMENTS

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Book review

Radionuclide Imaging Techniques. By Peter F. Sharp, Philip P. Dendy and W. Ian Keyes, pp. 271, 1985 (Academic Press Inc. London), £58.00/$63.50 Hardback, £29.50 Paperback.
ISBN 0–12–639020–7

This latest book in the *Medical Physics* series covers the fundamentals of radionuclide imaging and the current state of scientific and technical developments. It has been written by three physicists who have clearly given much thought to concepts and the logical presentation of relevant material. The result is a work which is refreshingly original and yet very practical.

The nature of "The Imaging Problem" is described in a chapter which presents the physical, mathematical and radiochemical principles illustrated by well chosen examples of applications. Imaging systems are explained with the help of many clear diagrams, and the development of the gamma camera is traced to the most recent advances. An interesting chapter devoted to "Other Imaging Devices" includes such developments as the semi-conductor array and the multiwire proportional chamber. Particular attention is given to the measurement of performance with full description of theory and practice and examples of modern results.

Tomography is covered with a concise account of reconstruction theory (including attenuation correction), and of practical implementations, including positron techniques. The chapter on image display includes a thorough treatment of image evaluation methods, describing the use of receiver operating characteristic (ROC) curves. Many aspects of data analysis are classified and explained, and a critical account of methods of quantifying radionuclide uptake is given. There is a good discussion on the evaluation of clinical effectiveness, in which problems of trial design, analysis of results and comparison of techniques are carefully considered. Finally, a thoughtful chapter on "The Future" echoes and amplifies the useful concluding remarks to previous chapters.

The authors have achieved consistent clarity of style, and succeed in presenting an up to date and well referenced review of the subject. It should be read by every physicist entering this field and will be useful to many (of whatever discipline) as a source of information, explanation and stimulation.

R. A. SHIELDS

1986, *The British Journal of Radiology*, 59, 609–610 JUNE 1986 •

Case reports

Congenital pleural effusion in Down's syndrome

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(*Received November 1985*)

Congenital pleural effusion can be diagnosed antenatally by obstetric ultrasound scan and contingency plans made for a skilled paediatric team to be present at delivery. The last two infants delivered in Leeds with congenital pleural effusion, diagnosed on obstetric ultrasound, had Down's syndrome. In neither case had the possibility of a chromosomal defect been considered.

CASE REPORTS

Case 1

This infant was born at term to a 20-year-old primigravida whose pregnancy had been uneventful until 34 weeks' gestation, when an ultrasound scan, carried out for polyhydramnios, revealed a right-sided pleural effusion. Two repeat ultrasound scans carried out at 34 weeks' and 36 weeks' gestation confirmed the presence of a large pleural effusion (Fig. 1). At birth the infant was oedematous but not hydropic, his haemoglobin was 17 g/dl, he was not in heart failure and there was minimal respiratory distress. He had the typical appearance of an infant with Down's syndrome. Thoracocentesis was not clinically indicated but a right-sided pleural effusion was confirmed on a chest radiograph (Fig. 2). An echocardiogram showed evidence of a large endocardial cushion defect and karyotyping confirmed the diagnosis of Down's syndrome of the translocation type (46 XY t (21 : 21)).

Case 2

This infant was born at 34 weeks' gestation to an 18-year-old primigravida whose pregnancy was uneventful until 28

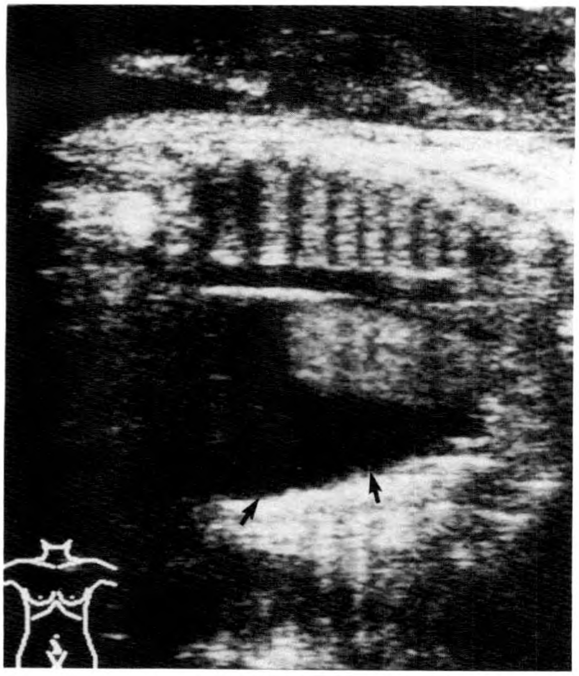

FIG. 1. *Case 1.*

Obstetric ultrasound at 34 weeks' gestation. The effusion is indicated by the black arrows.

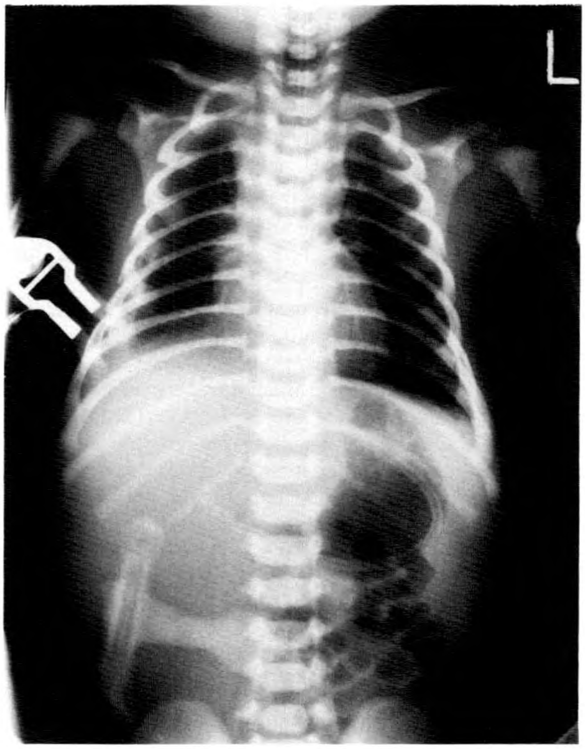

FIG. 2.

Chest radiograph showing right pleural effusion.

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weeks' gestation, when polyhydramnios developed. An ultrasound scan at this stage showed no fetal abnormality and the pregnancy continued uneventfully until the spontaneous onset of pre-term labour. A repeat ultrasound scan, carried out in view of persisting polyhydramnios, showed a left-sided pleural effusion. At birth the infant was blue, floppy and gasping (Apgar scores 4 at 1 min, 7 at 5 min) but responded to normal resuscitative measures. On examination the infant was not hydropic, there was reduced air entry on auscultation of the left chest and he had the typical features of Down's syndrome. Urgent chest radiography confirmed the presence of a large, left-sided pleural effusion and 60 ml of straw-coloured fluid (protein content 29 g/l) were aspirated from that side. An endocardial cushion defect was confirmed on echocardiography and karyotyping revealed a trisomy Down's (47 XY+21).

DISCUSSION

The association between Down's syndrome and congenital pleural effusion is not widely recognised. Yoss and Lipsitz (1977) described two infants with Down's syndrome and congenital chylothorax. Neither was hydropic and only one had a heart defect. An infant with Down's syndrome was among a series of 12 cases of congenital chylothorax reported at a meeting of the British Paediatric Association (Campbell et al, 1984). We know of no other reports. The association between Down's syndrome and congenital pleural effusion may be more common than realised and the diagnosis of Down's syndrome should be considered if a pleural effusion is detected on obstetric ultrasound.

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Intravascular papillary endothelial hyperplasia of the adrenal gland

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The efficacy of imaging the adrenal gland by means of computed tomography (CT) has been well documented (Hattery et al, 1981; Baba, 1982). Computed tomography can readily and accurately demonstrate both the normal and abnormal adrenal gland. This report describes the CT manifestations in a case of adrenal intravascular papillary endothelial hyperplasia.

Papillary endothelial hyperplasia (Clearkin & Enzinger, 1976) is a peculiar, benign intravascular process, which includes papillary structures composed of a single layer of swollen endothelial cells around a core of fibrous connective tissue and which simulates angiosarcoma histopathologically. Most such lesions are located deep in the dermis or subcutis without involvement of the overlying skin (Clearkin & Enzinger, 1976; Kuo et al, 1976; Rosai, 1981). They can occur in a variety of organs and with other lesions, such as in previously normal vessels or in varices, haemorrhoids, pyogenic granulomas and haemangiomas (Kuo et al, 1976; Rosai, 1981). However, involvement of the adrenal gland has not previously been documented.

CASE REPORT

A 60-year-old woman complained of occasional back pain of 1 year's duration, which was slowly progressive. On physical examination, including palpation, there was no evidence of a mass. The laboratory findings were normal. Plain abdominal radiography revealed a round, soft-tissue mass containing multiple, minute, discrete calcifications in the left upper quadrant (Fig 1). Comparison with an intravenous pyelogram performed 3 years previously showed an increase in the maximum diameter of the mass from 4.2 cm to 5.5 cm and an increase in the prominence of the calcifications. Abdominal ultrasonography revealed evidence of a left suprarenal mass

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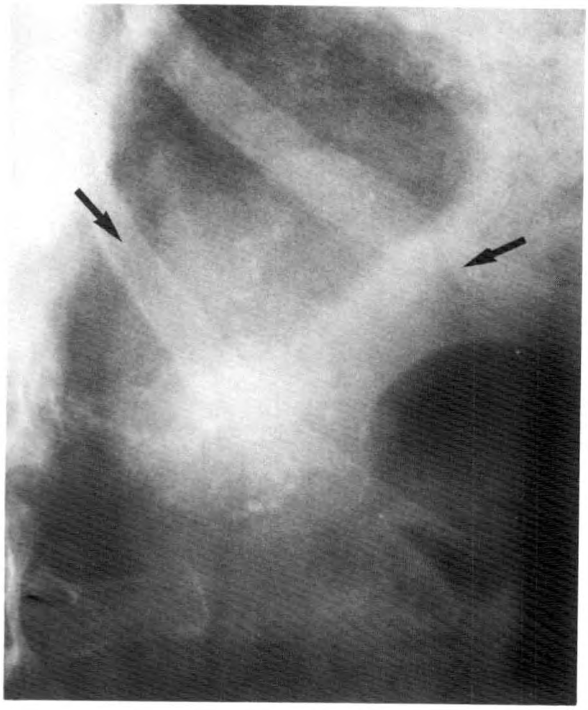

FIG. 1.
Multiple, discrete calcifications in a round, soft-tissue mass (arrows) in the left upper quadrant.

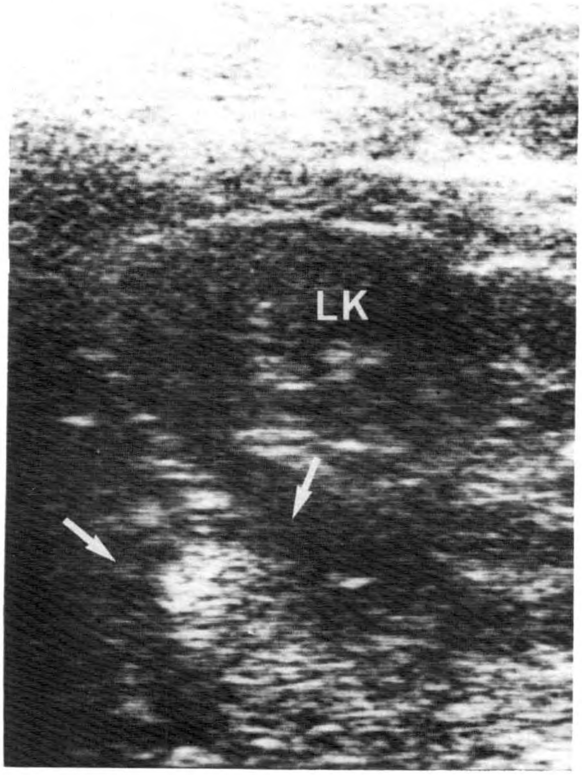

FIG. 2.
Posterior longitudinal real-time ultrasonogram shows a left suprarenal mass (arrows) which is highly echogenic centrally. LK = left kidney.

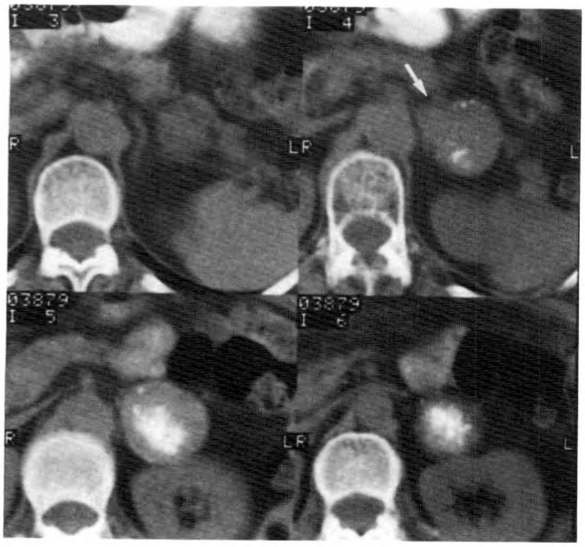

FIG. 3.
Sequential CT images (L + 50, W 1000) show the circumscribed, round mass (arrow), containing multiple, discrete calcifications, which apparently arises from the body and lateral limb of the left adrenal gland. A normal medial limb of the left adrenal gland is seen in the upper left scan.

which was highly echogenic centrally, with slight, distal acoustic shadowing (Fig. 2). A subsequent intravenous pyelogram showed the lesion to be superior and anterior to the left kidney, which was normal.

Computed tomography of the left retroperitoneal region demonstrated a well defined, 5 cm-diameter mass which apparently arose from the body and lateral limb of the left adrenal gland (Fig. 3). This lesion contained multiple calcifications whose CT attenuation value was 353 HU. Following the intravenous administration of a contrast medium, the lesion was poorly enhanced from 48 HU to 61 HU. Computed tomography clearly confirmed that the lesion was distinct from the body and tail of the pancreas, as well as the upper pole of the left kidney.

Electrolyte analyses, including those for calcium and phosphates, and biochemical examinations including catecholamines (epinephrine, norepinephrine and vanillylmandelic acid), cortisol, 17-hydroxycorticosteroid (OH), and 17-ketosteroid (KS) were all within the normal range. Adrenal scintigraphy showed no abnormality.

During a left total adrenalectomy, a dark, reddish mass was partially surrounded by a distended adrenal cortex. It did not adhere to any of the surrounding structures. It weighed 31 g and contained blood and multiple, minute, calculus-like components weighing in aggregate 17 g. On analysis, these were found to consist of 78% calcium phosphate and 22% calcium carbonate. This histological specimen revealed the

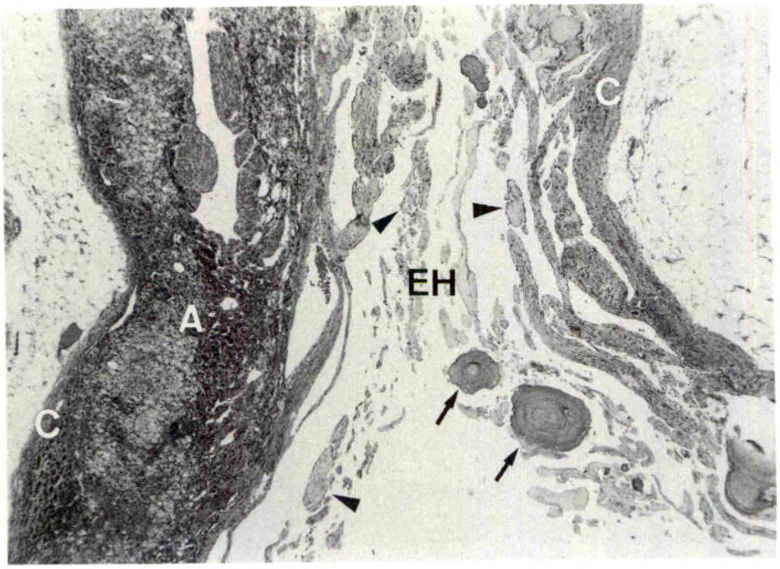

FIG. 4.

The microscopic specimen (×35) confirmed this mass to consist of intravascular papillary endothelial hyperplasia (EH) with dystrophic calcification (arrows). The papillary structures (arrowheads) were composed of a single layer of swollen endothelial cells surrounding a core of fibrous connective tissue. C = capsule of the left adrenal gland (A).

papillary structures to be composed of a single layer of swollen endothelial cells around a core of fibrous connective tissue in the left adrenal gland. This was indicative of intravascular papillary endothelial hyperplasia with dystrophic calcification (Fig. 4). The patient remains well 1 year after surgery.

DISCUSSION

Papillary endothelial hyperplasia is a peculiar, benign intravascular process that bears a remarkable histopathological resemblance to a haemangiosarcoma. Clearkin and Enzinger (1976) described features which aid in its recognition and in its differential diagnosis from a haemangiosarcoma. These include the intraluminal location of the lesion, the absence of tissue necrosis and the intimate association of the proliferated tuft-like structures with thrombotic material. The subcutis of the fingers, the head and neck regions and the trunk are its most common locations. It can occur either in previously normal vessels or in varices, haemorrhoids, pyogenic granulomas and haemangiomas (Kuo et al, 1976; Rosai, 1981). The lesion in the present case was located in the left adrenal gland but did not prove to be accompanied by a haemangioma.

Lee et al (1982) reported a case of adrenal haemangioma with phleboliths, in which there was no description of intravascular papillary endothelial hyperplasia. Clearkin and Enzinger (1976) suggested that thrombosis precedes the papillary proliferation and that the thrombotic material serves as a matrix for its development. Slowing of the blood flow, stasis and thrombosis, as in haemangioma, vascular malformations and dilated veins, appear to be the only prerequisites for the development of this lesion.

Computed tomography defines the anatomical contours, configuration and volume of a suprarenal mass effectively. To a certain extent, CT can help in assessing its general tissue characteristics. The CT image, however, is not specific as far as histopathology or tumour physiology (hormonal activity) is concerned. The range of attenuation values for adrenal masses varies. Attenuation differences have been attributed to varying constituents such as fat and/or intrinsic changes related to necrosis and haemorrhage (Schaner et al, 1978). Adams et al (1983) reported that size, contrast enhancement and consistency are significant discriminators for the CT image to differentiate malignant from benign adrenal masses. Hussain et al (1985) commented that irregular consistency of an adrenal mass did not add to the capability of predicting cancer when its size and contrast enhancement were known. The intravascular papillary endothelial hyperplasia in the present case appeared as a well defined, 5 cm-diameter, round mass, with relatively poor enhancement from 48 HU to 61 HU after the intravenous administration of contrast medium. The radiographic characteristics in the present case included multiple, discrete, minute calcifications in a well circumscribed, round mass. Histopathologically, the calcification is of dystrophic type, partly in thrombus and partly in the lesion itself, viz. an intravenous papillary endothelial hyperplasia. Underlying conditions in which calcification can occur include tuberculosis, spontaneous haemorrhage, adrenal cyst (Martin, 1965), myelolipoma, haemangioma, neuroblastoma, carcinoma and metastatic adrenal melanoma. Less frequently detected on plain radiography are phaeochromocytoma and adenoma and they are not associated with adrenal hyperplasia. Non-neoplastic disease of the adrenal gland, including intravascular papillary endothelial hyperplasia, can be detected with greater frequency using CT and ultrasonography. Although it is rare, intravascular papillary endothelial hyperplasia should

1986, *The British Journal of Radiology*, 59, 613–615

be considered in the differential diagnosis of adrenal masses. Its characteristic radiographic features, especially those observed on CT, should be borne in mind.

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Technetium-99m Medronate uptake in subcutaneous soft-tissue nodules in a patient with renal failure and renal adenocarcinoma

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Subcutaneous heparin preparations are often used for prophylaxis of post-operative deep venous thrombosis. We report a case in which uptake of the bone scanning agent $^{99}Tc^{m}$ methylene diphosphonate (Medronate) into subcutaneous heparin injection sites misleadingly suggested metastases from a renal adenocarcinoma.

CASE REPORT

A 45-year-old man with adult polycystic kidney disease reached end-stage renal failure. Thrice weekly hospital haemodialysis via radial arterio-venous fistula was the chosen method of treatment. During the following 7 months he suffered recurrent right loin pain with associated urinary tract infections and two episodes of bacteriologically confirmed septicaemia. Table I shows his pre-dialysis biochemical values during this time. Before including him in the UK Transplant

TABLE I

PATIENT BIOCHEMICAL ASSAY

	Pre-dialysis values*	Normal range
Urea (mmol/l)	33.5 (1.2)	2.5–7.0
Creatinine (μmol/l)	1489 (174)	60–120
Ionised calcium (mmol/l)	1.15 (0.04)	1.19–1.29
Phosphate (mmol/l)	2.05 (0.23)	0.80–1.40
Parathormone (IU/l)	2.1 (0.4)	<0.3–1.4
Alkaline phosphatase (IU/l)	179 (27)	110–295

* Results are expressed as mean values over 6 months with the standard deviation in parentheses.

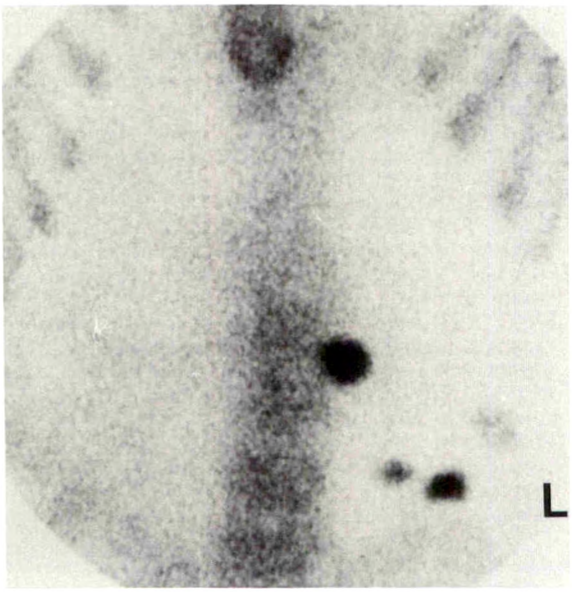

FIG. 1.

Anterior mid-trunk view on bone scan showing four spots of localised uptake in soft tissue in the left abdomen.

Programme it was decided to remove the right kidney. A 3 kg polycystic kidney was removed via a right loin incision. When sectioned, the kidney was found to contain a neoplasm more than 4 cm in diameter within its substance. Histology showed it to be a clear-cell carcinoma. Post-operative care included the use of heparin for prophylaxis against deep-venous thrombosis; 5000 units of calcium heparin (Calciparine, Sanofi UK Ltd) in water for injection adjusted to pH 7 with HCl or $Ca(OH)_2$ were injected subcutaneously into the anterior abdominal wall twice daily.

Three weeks after surgery, the patient reported the appearance of three tender nodules on his anterior abdominal wall. Clinical examination confirmed the presence of three discrete, hard, irregular subcutaneous nodules on the left anterior abdominal wall, suggestive of metastatic disease. A CT scan of the abdomen showed para-aortic node enlargement but no evidence of tumour in the remaining left, polycystic kidney. There was no evidence of skeletal metastases on a radionuclide bone scan obtained using $^{99}Tc^{m}$ Medronate. However, there were four areas of increased uptake on the scan, apparently localised to the three nodules on the abdominal wall and to one area which was not palpable (Fig. 1). The largest nodule was excised under general anaesthetic. It measured 23 mm × 10 mm × 3 mm and had the appearance of fibrofatty tissue with white flecks on its cut surface. Microscopy showed a foreign-body reaction with giant cells containing calcified material. Basophilic filaments in some cells stained strongly for phosphate, suggesting active calcium deposition, and there was some staining for iron. There were no histological features of malignancy and no evidence of pyogenic infection. Since removal of the tissue, the other clinically evident lesions have regressed.

DISCUSSION

Many soft-tissue abnormalities are known to show increased uptake of the radiopharmaceuticals used for bone scanning. This extraosseous localisation has been reported in various primary and secondary tumours (Nolan, 1974; Merrick, 1975; Ghaed & Marsden, 1978; Heck, 1980; Vorne & Saukko, 1984) including recurrent renal-cell carcinoma (Ozarda et al, 1983), and in metastatic calcification (Richards, 1974) and ischaemic (Wraight, 1983) and infarcted tissue (Buja et al, 1977). Iatrogenic soft-tissue radionuclide accumulation has been reported in relation to iron dextran injections (Byun et al, 1976) and after surgery (Poulose et al, 1975). The mechanism of accumulation in such cases is debatable. In contrast, localisation of the radiopharmaceutical in bone is related to the rate of mineralisation and the blood flow to the site (Charkes, 1979; Fogelman, 1980).

Ectopic calcification is a well recognised problem in patients with end-stage renal failure. This patient had no evidence of this process before surgery and his biochemical abnormalities are not considered sufficiently severe to explain such calcification on their own. The microscopic picture in this case suggested active calcium deposition in a foreign-body reaction to a filamentous material. This is known to occur in response to surgical suture material, but these nodules were a considerable distance from the nephrectomy scar and there was no radionuclide uptake around the scar itself. From the location of the nodules we suggest that they were due to a reaction to the subcutaneous injection of calcium heparin.

The mechanism of the proposed reaction involves the combination of disordered mineral metabolism found in renal failure and the local effects of the injected calcium heparin. Metastatic calcification in uraemic patients is dependent on a variety of factors: the calcium × phosphate product, the degree of secondary hyperparathyroidism, hypermagnesaemia, alkalosis and local tissue injury (Massry & Coburn, 1976). This patient had a normal serum magnesium level and was not alkalotic. However, the subcutaneous injection of calcium heparin would increase the local calcium × phosphate product and cause tissue injury. Coupled with the mild secondary hyperparathyroidism, this is probably sufficient to explain the calcification in the subcutaneous nodules. Methylene diphosphonate not only attaches to calcium phosphate but also binds to the denatured proteins found in ischaemic tissues and to alkaline phosphatase enzymes (Brill, 1981). Ischaemia and increased cellular enzyme activity may also have been involved in the localisation of the $^{99}Tc^{m}$ Medronate within the lesions in this patient.

This case presents yet another cause of abnormal radiopharmaceutical distribution in a clinical situation. It also demonstrates that iatrogenic soft-tissue reactions can mimic metastatic disease clinically.

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Menetrier's disease in childhood associated with cytomegalovirus infection: a case report and review of the literature*

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Menetrier's disease is a rare disorder first described in 1888 (Menetrier, 1888). It is characterised by giant hypertrophic gastritis and protein-losing enteropathy. In adults the disease has a chronic course with a risk of developing gastric carcinoma (Scharschmidt, 1977). However, Menetrier's disease is much rarer in childhood and usually runs a benign course (Burns & Gay, 1968). The aetiology is unknown but five previously reported cases have been associated with cytomegalovirus (CMV) infection (Lachman et al, 1971; Leonidas et al, 1973; Buts et al, 1978; Floret et al, 1978; Stillman et al, 1981). We report a further case in which CMV was also isolated and discuss the role of this agent in the aetiology. We stress the value of radiology rather than biopsy in the diagnosis and management of the disease in children.

CASE REPORT

A previously well 4-year-old boy presented with a 1-week history of coryzal symptoms, vomiting and anorexia. He had on one occasion passed a small melaena stool but his bowel motions had been otherwise normal. Two days prior to admission his mother noticed that his face, abdomen and legs had become swollen. He had not been on any medication and there was no family or past history of atopy. The other members of his family were asymptomatic.

On examination he was afebrile but had moderate oedema of the face and legs with ascites and hepatic enlargement 2 cm below the right costal margin. There was dullness to percussion and reduced air-entry at both lung bases.

Investigations revealed the following: haemoglobin 13.8 g/dl, white cell count 10.6×10^9/l, neutrophils 46%, lymphocytes 50%, monocytes 1%, eosinophils 3%, platelets 245×10^9/l. A blood film showed occasional atypical lymphocytes, monospot negative and ESR 22 mm/h. Urea level was 4.7 mmol/l, creatinine 56 μmol/l, total protein 34 g/l, albumin 16 g/l and globulins 18 g/l.

Liver function tests showed a total bilirubin of < 5 mmol/l, gamma-glutamyl transpeptidase 7 IU/l, alkaline phosphatase 135 IU/l, aspartate transaminase 38 IU/l and alanine transaminase 13 IU/l. A faecal occult blood test was negative and no ova cysts, parasites or pathogens were found in the stools. Urine: no significant growth, microscopy normal, trace of protein. Urinary vanillylmandelic acid excretion was normal.

A chest radiograph showed a right-sided pleural effusion which initially increased in size a week later and then resolved completely by 3 weeks. Abdominal ultrasound also revealed right-sided pleural effusion and a moderate degree of ascites. No mass lesion was seen. The liver and both kidneys appeared

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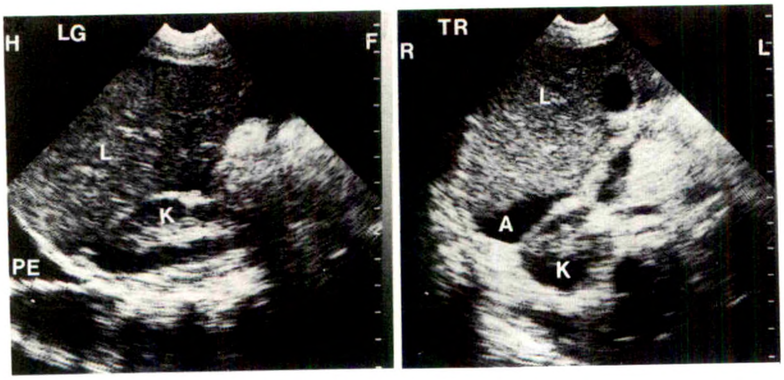


Fig. 1.

Abdominal ultrasound. Supine longitudinal (LG) and transverse (TR) scans revealing right-sided pleural effusion (PE) and ascites (A). Normal liver (L), gallbladder and right kidney (K).

normal (Fig. 1). An intravenous urogram was normal with very good function in both kidneys. A skeletal survey showed no abnormality.

A diagnostic tap was performed of the ascitic fluid which had a protein content of 1.7 g/l and no growth on culture. Cytology on a cytocentrifuged specimen revealed clumps of atypical cells which were thought to be malignant, with scanty cytoplasm and large nuclei with prominent, coarse chromatin. No intracellular inclusions were seen. A ^{51}Cr-labelled albumin test was performed which showed 20.1% of the injected dose excreted in the stool over a 5-day period (normal value < 1%). A diagnosis of protein-losing enteropathy was made and he was started on supportive treatment with a high-protein, low-salt diet. A barium-meal examination demonstrated very prominent and abnormally enlarged, huge gastric mucosal folds in the fundus and body of the stomach but sparing the antrum. No ulcer crater was seen and the soft, pliable, giant mucosal folds did not conform to any specific pattern. No mass lesion was evident (Fig. 2A). The oesophagus was normal with uniform regular mucosal folds and there was no evidence of oesophageal varices. The barium follow-through showed normal, undilated small intestine with normal-sized, regular mucosal folds of the jejunum and the ileum (Fig. 2B).

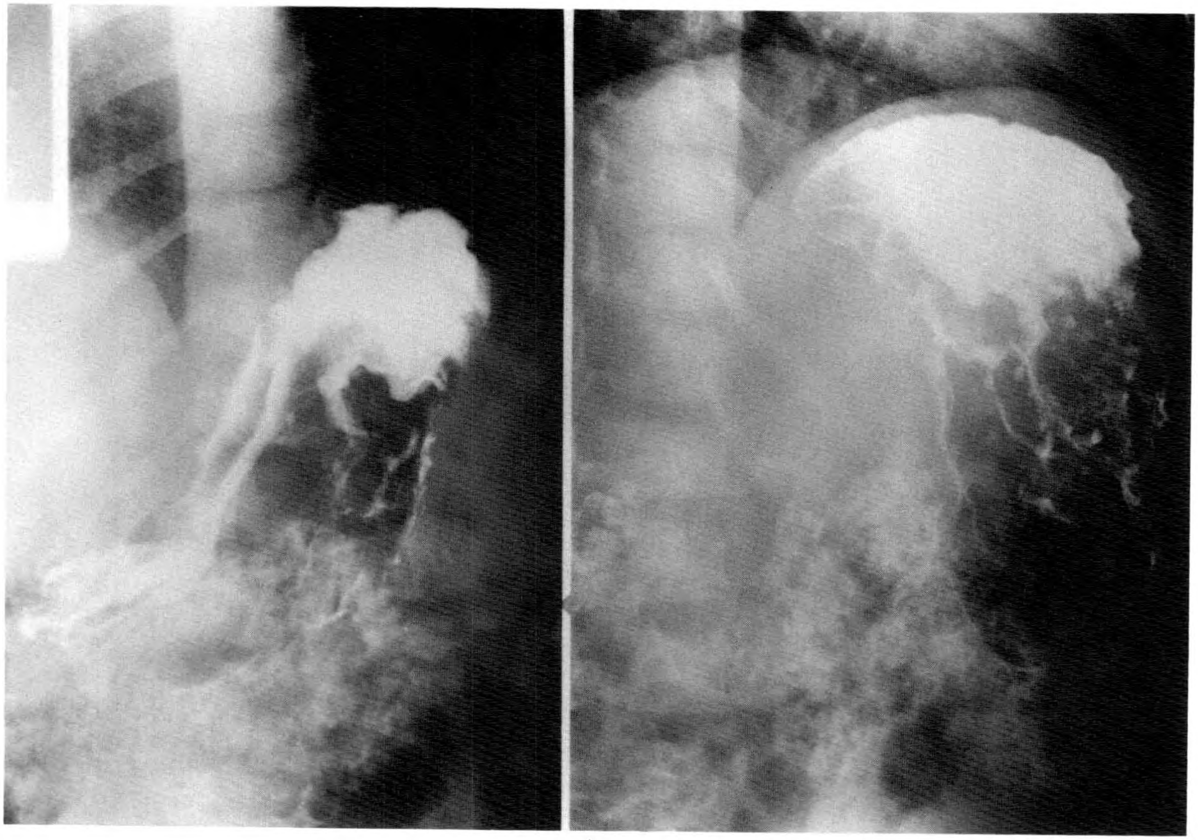
In view of the atypical cells present in the ascitic fluid, laparotomy was planned but 10 days after admission the patient's general condition improved on supportive dietary

TABLE I

Clinical features, investigations and outcome in 23 patients with menetrier's disease

Reference	Age (years)	Symptoms	Duration (weeks)	Albumin/ globulin (g/l)	Hb (g/dl)	Eosinophil count %	Biopsy	Outcome
Degnan & Montclair, 1957	3	NVOA	1	25/14	9.8	19	ND	Recovery 3 weeks
Schroder, 1961	10	NVPOA	1	26/14	11.6	3	+	Recovery 4 weeks
Pittman et al, 1964	5	NVO	1.5	16/10	13.3	5	+	Recovery 3 weeks
Schuster, 1967	5	NVHPO	?	25/43	9.5	?	+	Gastrectomy for bleeding
Herskovic et al, 1968	6	NVDPOA	0.5	24/07	14.5	8	+	Recovery 10 weeks
Burns & Gay, 1968	9	VP	6	44/24	10.8	7	ND	Recovery 4 weeks
Lachman et al, 1971	8	NVH	16	18/24	10.7	?	Post-mortem	Gastrectomy, ? lymphoma Died renal failure.
Lachman et al, 1971	9	VPOA	1	20/10	ND	19	+	Recovery 4 weeks
Lachman et al, 1971	7	NVPO	3	16/20	ND	10	+	Recovery 4 weeks
Sandberg, 1971	4	NVPOA	2	15/28	14.4	7	+	Recovery 2 weeks
Leonidas et al, 1973	3	O	2	19/16	14.6	2	+	Recovery 4 weeks
Gwinn & Lee, 1976	5	OA	1	25/16	14.5	9	ND	Recovery 3 weeks
Newman et al, 1976	3	NVPHO	8	14/31	6.8	7	+	Recovery 8 weeks
Burrell et al, 1979	4	NOA	1.5	16/16	11.0	20	ND	Recovery 4 weeks
Floret et al, 1978	2	V	1	20/10	9.4	5	+	Recovery 8 weeks
Buts et al, 1978	4	VO	0.5	44 total	13.9	15	ND	Recovery 8 weeks
Casenave et al, 1980	3	VHO	2	18/18	13.8	1	ND	Recovery 4 weeks
Kraut et al, 1981	11	P	16	30/–	5.4	15	+	Gastrectomy for bleeding
Kraut et al, 1981	7	NVDA	1.5	19/22	13.6	13	+	Recovery 2 weeks
Chouraqui et al, 1981	8	NVPO	1.5	17/16	13.2	*	+	Recovery 2 weeks
Stillman et al, 1981	3	POA	1	19/14	14.3	6	+	Recovery 3 weeks
Stillman et al, 1981	5	DPO	2	17/12	14.8	11	+	Recovery 1 week
Coad & Shah (present study)	4	VOA	1	16/18	13.8	3	ND	Recovery 2 weeks

N nausea, V vomiting, D diarrhoea, P pain, H haemorrhage, O oedema, A ascites, ND not done, *given as absolute value of 420/mm^3.



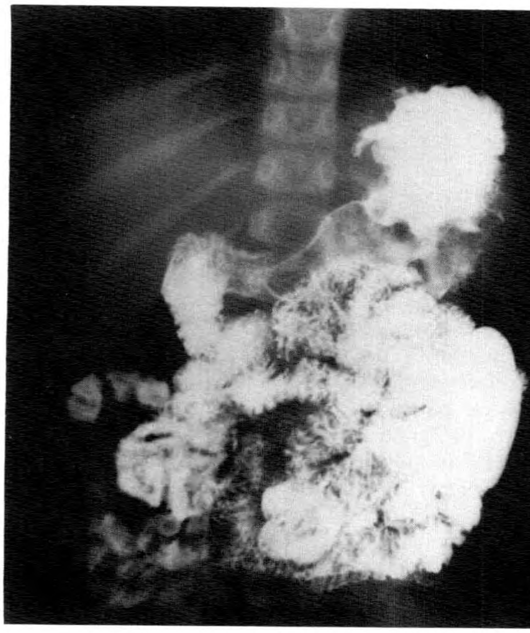


FIG. 2.

(A) Barium-meal examinations demonstrate very prominent and abnormally enlarged, huge gastric mucosal folds in the fundus and the body of the stomach, but sparing of the antrum. The rather poor coating of the mucosa is due to presence of an excess of mucus and the gastric secretion. (B) Barium followed through the small intestine shows normal, undilated loops of bowel with normal-sized, regular mucosal folds of the jejunum and the ileum.

treatment and he lost 3.5 kg in weight over a 5-day period, with resolution of the oedema, ascites and pleural effusion. He was subsequently discharged from hospital and followed as an outpatient, since when he has been well apart from a transient recurrence of the oedema associated with an upper respiratory tract infection. When seen 6 months after presentation he was quite well with no abnormal physical signs. Follow-up barium-meal examinations were carried out at 3 months and 6 months. At 3 months there was considerable improvement in the appearances of the gastric mucosal folds with reduction in their size and by 6 months normal appearances were observed (Fig. 3). Cytomegalovirus was finally isolated from the urine a month after diagnosis and rising titres of complement-fixing antibodies to CMV were estimated in the blood as follows. Admission 1/64, 2 weeks > 1/264, 4 weeks 1/256, 6 weeks 1/32.

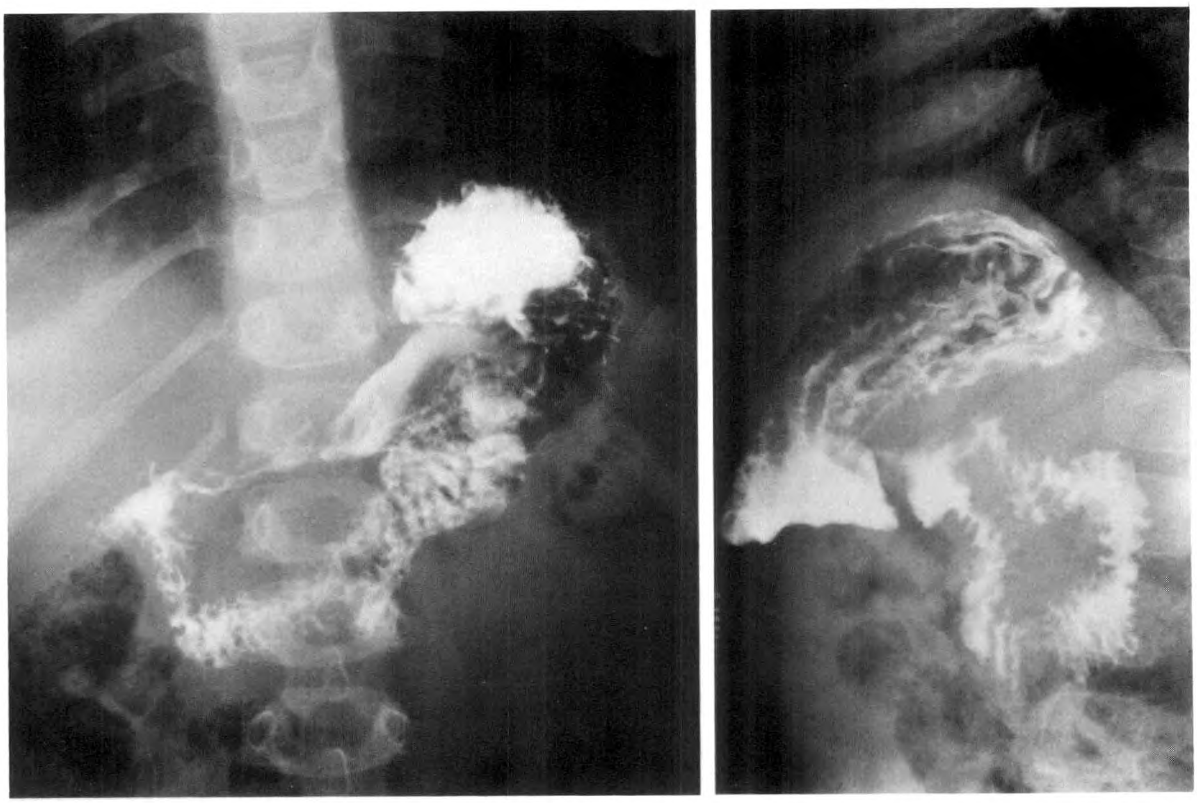


FIG. 3.

Follow-up barium meal examination at 3 months shows considerable improvement in the appearances of the gastric mucosal folds with reduction in their size and uniform, normal pattern.

REVIEW

A review of the literature revealed 22 previously reported cases. The clinical features, investigations and outcome in these and our patient (23) are shown in Table I. There were 13 boys and 10 girls, all were aged 11 years or younger and the majority (14) were less than 5 years old. The duration of symptoms was generally less than 3 weeks but in three patients was 2–4 months. Common presenting symptoms and signs were nausea and vomiting (18), abdominal pain (12) and oedema and ascites (19), although four patients had neither of the latter signs. Haemorrhage was a presenting feature in five patients and anaemia was found in five. Sixteen children had a mild to moderate eosinophilia. The plasma albumin levels were less than 30 g/l in all but one child and less than 20 g/l in 16 children. Gastrointestinal protein loss was demonstrated in eight of nine children tested by various methods and gastric protein loss found in two patients. Gastric acid output was reduced or absent in five of six patients studied. Hypertrophic gastropathy was shown radiologically in all of the children and eight children had pleural effusions. The diagnosis of Menetrier's disease was confirmed by biopsy in 16 cases; these were obtained by endoscopy (nine), laparotomy (six) and at post-mortem examination in one child. Biopsy was not performed in seven cases.

The histological features included gastric glandular hypertrophy, basilar cysts and intestinal inflammatory reaction of eosinophils, lymphocytes and plasma cells. Treatment was generally supportive, with a high-protein diet. Two patients had a gastrectomy performed to control bleeding (Schuster, 1967; Kraut et al, 1981) while a third child had a gastrectomy for suspected lymphoma and died of renal failure (Lachman et al, 1971). The majority of patients (16), however, recovered spontaneously within 1 month of diagnosis and all but one of the survivors had recovered by 2 months. A total of six children in these studies had positive evidence of CMV infection (Table II) in blood (four), urine (three) and gastric biopsy specimens (three), although in the majority of children no virological studies were reported. Parainfluenza virus was obtained from the nasopharyngeal secretions of one child (Herskovic et al, 1968).

DISCUSSION

The aetiology of Menetrier's disease in childhood is, as yet, not clearly understood. A hypersensitivity reaction is suggested by the presence of an eosinophilic

TABLE II

Cases of CMV infection and method of diagnosis

Reference	Serology	Urine	Gastric biopsy
Lachman et al, 1971			+
Leonidas et al, 1973	+		
Floret et al, 1978	+	+	
Buts et al, 1978	+		
Stillman et al, 1981		+	+
Coad & Shah (present study)	+	+	

infiltration in the gastric mucosa which resolves on recovery, a peripheral eosinophilia and elevated IgE levels despite depression of other immunoglobulin classes. However, a family or past history of allergy is uncommon and in the two cases where RAST tests have been performed these have been negative to common food allergies (Stillman et al, 1981). It has been postulated that viral infections contribute to the development of allergic sensitisation by preferentially depressing IgE T-cell suppressor cells, thus allowing helper IgE T-cells to stimulate IgE production (Frick et al, 1979). Gastrointestinal viral infections may also be locally cytopathogenic, possibly allowing mucosal penetration of allergens which then stimulate a hypersensitivity reaction. If this is the case, however, the target allergens remain unclear from the available data and further studies are required. The occurrence of acute cytomegalovirus infection concurrently with this rare syndrome is probably not fortuitous and this is supported by the observations of an association in five previous cases (see Table II).

The differential diagnosis includes many other conditions which are distinguishable in the majority of cases on clinical and radiological grounds. Gastric lymphomatous infiltration is rare in childhood and usually associated with generalised disease and an unrelenting course (Pickett & Briggs, 1967). No primary gastric lymphomas were found in a review of 144 cases of lymphoma in patients under the age of 15 years (Jones & Klinberg, 1963) and no cases in patients under 20 years were reported in a review of 346 primary stomach lymphomas (Freeman et al, 1972). The barium meal should distinguish the rigid folds associated with infiltrative lymphoma but a full-thickness biopsy is required for definitive diagnosis. Patients with eosinophilic gastroenteritis (Cello, 1979) may present in a similar manner with nausea, vomiting, abdominal pain and bleeding; protein-losing enteropathy is, however, only occasionally found. The majority of patients have a family history of allergic disorders and a peripheral blood eosinophilia of up to 55% may be found. The radiological findings are similar but the disease may also involve the gastric antrum and small intestine. There is extensive infiltration of the mucosa and the muscularis mucosae of the stomach with a predominantly eosinophilic infiltrate. The disease is a chronic condition characterised by a prolonged relapsing course requiring treatment with steroids if an elimination diet to identify a food allergen is unsuccessful (Cello, 1979). Hypertrophic hypersecretory gastritis is a chronic condition associated with gastric acid hypersecretion and only rarely with protein-losing enteropathy (Brooks et al, 1970; Overholt & Jeffries, 1970). The Zollinger–Ellison syndrome has also been associated with hypertrophic hypersecretory gastritis but not with protein-losing enteropathy (Brooks et al, 1970). Crohn's disease of the stomach is almost always associated with other lesions in the gastrointestinal tract and pursues a chronic course (Beaudin et al, 1973). In contrast to adults with Menetrier's disease, who have prolonged disease with a significant risk of developing gastric carcinoma (Scharschmidt, 1977) children have a transient illness of acute onset which resolves spontaneously in most cases. Menetrier's disease should be diagnosed on clinical and radiological grounds and a biopsy reserved for those cases that are atypical or which do not resolve spontaneously. Both allergy and viral infections, particularly CMV infection, have been implicated in the aetiology but full viral and immunological studies should be performed in an effort to improve understanding of the disease.

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Fatal acute vasculitis after high-dose urography with iohexol

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The introduction of low-osmolar contrast agents such as iohexol has significantly reduced the incidence of adverse reactions in patients having intravenous urography. To our knowledge, there have been no deaths associated with the use of this drug reported to date. We describe a patient who developed a fulminating peripheral vasculitis 48 h after high-dose urography using iohexol. Death occurred 13 days later.

CASE REPORT

A 69-year-old female with a 20-year history of hypertension and associated mild chronic renal failure was admitted for investigation of anaemia and sudden deterioration in her renal function.

The hypertension had been controlled for the last 4 years with hydralazine (100 mg daily), atenolol (100 mg daily) and Navidrex K (Ciba Laboratories). Three months before admission a positive antinuclear factor (ANF) titre was noted (IgG titre 1/10 000, DNA binding 35%), thought to be related to the hydralazine. Although the patient showed no features of the lupus syndrome, the drug was discontinued shortly after admission.

To investigate the progressive renal insufficiency, high-dose intravenous urography was carried out using 100 ml of iohexol (Omnipaque 350, Nyegaard). There was no immediate reaction to the contrast medium. Opacification was very poor in each kidney, but contrast medium was present in the bladder at 2 h. There was no evidence of renal-tract obstruction.

Forty-eight hours later the patient developed marked periorbital oedema and a maculopapular rash over the shins, thighs, shoulders and forearms. This was associated with palpable purpura on the thighs. Over the next 24 h the rash became bullous and haemorrhagic and rapidly progressed to the formation of large, necrotic ulcers. The eyes were severely affected in a typical Stevens–Johnson manner, with conjunctivitis and periorbital oedema. This ultimately progressed to necrosis of the upper eyelids. Skin biopsy at this time showed an intense inflammatory vasculitis at all levels of the dermis involving arterioles, capillaries and venules.

On the fifth day the patient developed pulmonary oedema, associated with further deterioration of renal function. The skin and eye lesions became worse. High-dose steroid therapy and peritoneal dialysis were commenced, but the patient's general condition continued to deteriorate. *Klebsiella* septicaemia developed, and the patient died 13 days after urography.

Post-mortem examination, carried out at the request of H. M. Coroner, confirmed multiorgan involvement in the vasculitic process.

DISCUSSION

The clinical picture of an acute inflammatory vasculitis developing after the administration of an iodine-based contrast agent is compatible with acute iodism (Sumner et al, 1951). This is a very rare drug reaction, usually encountered following the administration of oral potassium iodide or iodised oils in bronchography (Scadding, 1934), although there has been one case report of a similar but less severe reaction following intravenous urography in an oliguric patient (Heydenreich & Olholm Larsen, 1977).

In the case we present there is no direct evidence that the vasculitis was due to iodine sensitivity. It could equally have been due to sensitivity to the entire iohexol molecule. Also, the picture is complicated by the hydralazine-related positive ANF. This drug is known to cause a lupus-like syndrome in a significant number of patients even at a low dose (Perry, 1973). A peripheral vasculitis proceeding to necrotic ulceration has also been reported (Bernstein et al, 1980; Taberner et al, 1981). Although the hydralazine-induced lupus syndrome is not usually associated with renal failure, there are some reports of hydralazine-associated glomerulonephritis (Bjorck et al, 1983; Kincaid-Smith & Whitworth, 1983).

However there are factors against this case being a reaction to the hydralazine. Firstly, the patient had no previous clinical features of the lupus syndrome. About half of patients taking hydralazine develop positive antinuclear factor titres and most do not develop the lupus syndrome (Cameron & Ramsey, 1984). Secondly, the speed of onset and severity of the vasculitis in this case is quite unlike the hydralazine-induced syndrome, which is characterised by a more insidious onset, a relatively benign course and spontaneous resolution when the drug is withdrawn. In this instance, the rash appeared 48 h after the hydralazine had been stopped.

Two further possibilities cannot be completely discounted. The incipient lupus syndrome may have been exacerbated by the contrast medium. Alternatively, the incipient lupus may have precipitated acute iodine sensitivity. We are not aware of any association between connective-tissue disorders and iodine-based contrast agents, but there is one recent case report of an exacerbation of known systemic lupus erythematosus, following metrizamide lumbar myelography (Gelmers, 1984).

Iohexol is a relatively new drug. Because of low toxicity and a low incidence of allergic reactions, it is recommended for intravenous urography in "high-risk" patients, such as those with chronic renal failure (Dawson et al, 1984; Grainger, 1984). We present this case because it demonstrates a very unpleasant and, in this instance, fatal adverse reaction following 48 h after the injection of this drug. We would be very interested to learn of any other cases where patients with a connective-tissue disorder have developed similar reactions.

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Book review

Nuclear Imaging in Pediatrics By Aslam R. Siddiqui, pp xi+288+index, 1985 (Year Book Medical Publishers, Inc., Chicago), £43.00.
ISBN 0-8151 7679-1

The role of nuclear medicine in paediatric practice is now well established. Very few departments, however, have facilities dedicated to that use for children. Children are, therefore, examined in general units. Paediatric patients will represent a small proportion of the total workload. It is, therefore, important to have a reference text available in a department, both to provide practical guidance for the technicians and as a refresher for the doctors as to the nature of paediatric pathology Dr Siddiqui's book is one of three specialised texts on paediatric nuclear medicine and to a large extent fulfills this requirement

There are 11 chapters. The first deals with practical hints on scanning and details of radiation doses. The remaining 10 describe the role of nuclear medicine in each of the major body systems—GI . . GU etc. The style throughout the book is consistent. Each chapter follows the same format, a history of the radiopharmaceutical, an imaging protocol and then an account of the clinical applications. The images are clear, the text readable and references up to date. Gallium imaging is dealt with in detail but there is but a brief mention of indium-labelled white cell scanning and this, I feel, should be covered in more depth in 1985.

Having read the text, one would know what can be done by nuclear imaging techniques in paediatric practice. There is, however, only limited discussion of the relative roles of ultrasound, CT and nuclear medicine in the management of clinical problems and I would have preferred to see more positive guidance given as to the order in which the various imaging techniques should be employed so as to minimise unnecessary investigation and irradiation. This is perhaps best exemplified in the chapter on brain imaging. Ultrasound and CT have virtually replaced nuclear imaging in the paediatric brain. Much of the information in it is now superfluous.

Dr Siddiqui's book reflects the practice of nuclear medicine in North America. Most British practice is the same and, therefore, the book is relevant to British departments. It compares adequately with the other two texts on paediatric nuclear medicine and can be recommended as a bench book in nuclear medicine departments. It would also be very useful in a hospital library for reference both by paediatricians and radiologists. The book will not inspire but will inform.

HELEN CARTY

1986, *The British Journal of Radiology*, 59, 623–624

JUNE 1986

Case of the month

Diagnosis of a right iliac fossa mass by computed tomography

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(*Received June 1984 and in revised form January 1986*)

CASE HISTORY

A 68-year-old woman presented with a 3-day history of vague, colicky abdominal pains. She had attended her local practitioner with similar pains for several years and was treated with laxatives. On examination she was generally well with a soft, ill-defined mass in the right iliac fossa. Plain abdominal radiographs revealed no abnormality. A CT scan (Philips Tomoscan 310) of the region was performed (Fig. 1) and a density profile through the mass was obtained (Fig. 2). Surgical management and subsequent histopathology confirmed the findings on CT.

Questions

(1) What is the diagnosis?

(2) What is the aetiology?

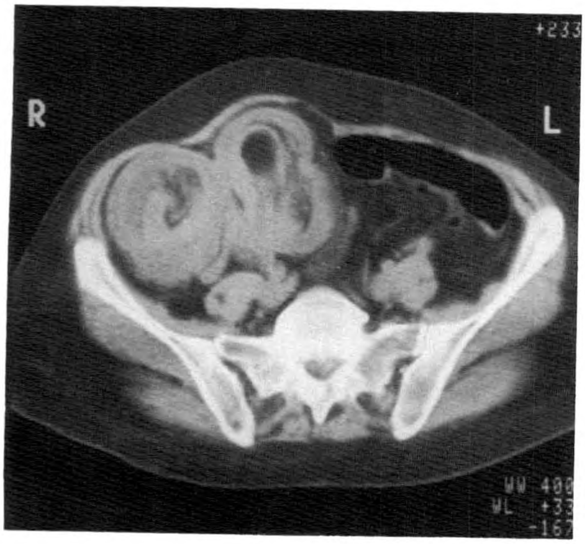

FIG. 1.

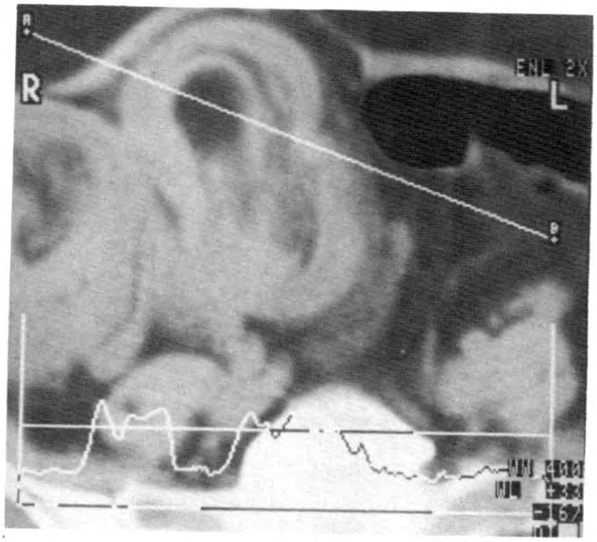

FIG. 2.

Requests for reprints to: M. Braithwaite, M.R.C.P., F.R.C.R., Department of Radiology, North Staffordshire Royal Infirmary, Stoke-on-Trent, Staffordshire.

DISCUSSION

Diagnosis

The diagnosis is ileo-colic intussusception. Four reports of diagnosis of intussusception by CT have appeared in the world literature (Parienty et al, 1981; Curcio et al, 1982, Donovan & Goldman, 1982; Styles & Larsen, 1983). Curcio et al and Donovan and Goldman have reported single cases of diagnosis of intussusception by CT and they describe several characteristic radiological signs. The overall appearance is one of a complex, "whorled" pattern of bowel loops with a distended loop of bowel (the intussuscipiens) encompassing the following features.

1. (1) The intussusceptum, viewed as a "sausage-shaped" soft-tissue component, often eccentrically placed because the infolding loop is forced into an off-centre position due to the mesentery also entering the lumen.
2. (2) A crescentic or wedge-shaped, low-density, intraluminal mass representing the invaginated mesentery.
3. (3) A leading mass may be seen or delineated by air or contrast medium.

Aetiology

The leading mass of the intussusception is a benign submucous ileal lipoma. The homogeneous, low-density mass within the lumen of a distended bowel loop is clearly seen in both figures. The density profile confirms negative density values identical to subcutaneous and mesenteric fat. Liposarcoma is unlikely due to the homogeneity and discrete, encapsulated appearance of the lesion.

Adult intussusception usually presents with chronic symptoms and diagnosis, though often delayed, is usually made with conventional radiography. While we cannot advocate CT as a primary diagnostic tool, experience with this case and others in the literature demonstrates the capabilities of CT in a condition where diagnosis is often elusive. Among the many applications of CT, localisation and characterisation of abdominal masses are most useful. A combined approach with ultrasonography is particularly helpful as an area of interest can be delineated (and, if appropriate, indicated with markers on the patient), enabling CT to be localised. This permits thinner sections with less separation than would be usual if the whole abdomen were to be scanned.

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Short communication

Protection of mouse chromosomes against whole-body gamma irradiation by SH-compounds

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Of the several chemicals considered for radioprotection, WR-2721 (S-2-(3-aminopropylamino)phosphorothioic acid), a derivative of cysteamine, has been found to be the most effective in protecting mammals (Yuhas et al, 1980). Another synthetic compound, MPG (2-mercaptopropionylglycine), has attracted attention since Sugahara et al (1970) discovered that it protects mammals against radiation death at a very low, non-toxic dose of 20 mg/kg body weight, which is optimal for protection. Most of the studies with these compounds have taken lethality and tissue injury as the end-points and very little is known about their effects on the genetic material. Experiments were, therefore, performed to study the protective effect of WR-2721 and MPG individually on the bone-marrow chromosomes of adult mice when administered before acute whole-body exposures.

MATERIALS AND METHODS

Colony-bred adult male mice, 8–10 weeks old, weighing 22–25 g, were injected with double-distilled water (control), 20 mg/kg MPG or 400 mg/kg WR-2721 intraperitoneally (experimental) before whole-body exposure to 0.5, 1.5, 3.0, 4.5 or 6.0 Gy of γ radiation from a ^{60}Co beam therapy source at a dose-rate of 72 cGy/min. The aqueous drug solutions were freshly prepared and injected 15–20 min (MPG) and 30–45 min (WR-2721) before irradiation. Twenty-four hours after exposure, six animals from each group were sacrificed and routine metaphase plates were prepared from the femoral bone marrow (colchicine pre-treated), stained with 4% Giemsa and analysed for chromosome changes. Six hundred metaphases were scored for each point. A cell containing 10 or more aberrations was taken to be severely damaged.

RESULTS

Both the control and experimental animals showed qualitatively similar types of aberrations. The major types identified were chromatid and chromosome breaks, and asymmetrical changes represented by acentric fragments, dicentrics, rings and multiple exchanges. Polyploidy was also scored. The frequency of aberrant cells as well as the number of aberrations/100 cells increased with the exposure dose (Table I). The percentage of aberrant cells for sampling at 24 h showed a linear relation to dose (Fig. 1). A similar pattern of changes was observed in both drug-treated groups, though the percentage of aberrant cells was significantly lower than in the control at all doses (Table I). Taking percentage aberrant cells for 0.5 Gy as the base, the dose reduction factor for MPG was calculated to be 2.6 and that for WR-2721 to be 4.5.

At the low exposures the number of exchange aberrations was lower than the chromosome and chromatid breaks. As the radiation dose was increased, the former increased very rapidly after 3 Gy and reached 1.5 times the latter in the higher-dose groups; at these doses, the severity of lesions also increased as indicated by the large number of pulverised and severely damaged cells. Both drugs were able to reduce these lesions. WR-2721 completely checked the pulverising effect of the radiation even after the highest exposure (6 Gy); severely damaged cells were also few in this group compared with the control and MPG-treated animals (Table I).

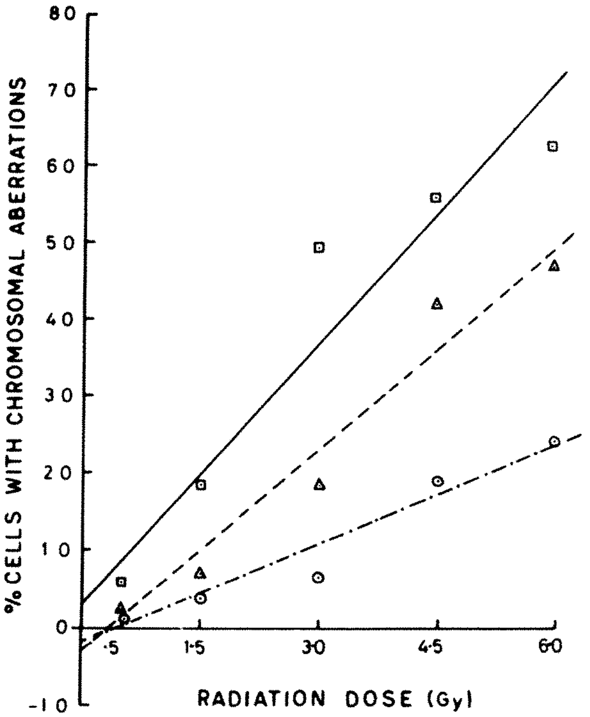

FIG. 1.

Percentage of aberrant cells as a function of the exposure dose drawn on the regression line. ☐ Irradiated controls, △ MPG (20 mg/kg) + irradiation, ⊙ WR-2721 (400 mg/kg) + irradiation.

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TABLE I

FREQUENCY OF CHROMOSOMAL ABERRATIONS AT 24 H IN THE CONTROL AND DRUG-TREATED MICE EXPOSED TO GAMMA RADIATION

Radiation dose (Gy)		Percentage of aberrant cells ±SE	Types of aberration		Aberrations/ 100 cells	Severely damaged cells	Cells showing pulverisation
			Breaks	Exchanges*			
0.5	C	6.00±0.86	25	14	6.5	0	0
	E_M	2.33±0.21 ($p < 0.002$)	13	1	2.3	0	0
	E_W	1.33±0.42†	12	2	2.3	0	0
1.5	C	18.67±2.13	74	64	23.00	2	1
	E_M	7.00±0.86†	40	54	15.66	2	0
	E_W	4.00±0.69†	29	7	6.00	0	0
3.0	C	49.67±1.53	195	464	109.83	59	21
	E_M	18.33±0.96†	99	134	38.83	18	0
	E_W	6.50±0.50†	21	32	8.83	0	0
4.5	C	55.67±3.04	272	399	111.83	121	12
	E_M	42.17±2.21‡	223	208	71.83	30	0
	E_W	19.17±0.95†	108	117	37.5	5	0
6.0	C	62.67±7.07	274	404	113.00	119	30
	E_M	47.17±3.29 (NS)	243	264	84.5	60	20
	E_W	24.17±4.54†	139	136	45.83	10	0

Percentage of aberrant cells in normal untreated mice = 0.33±0.18.
Total number of metaphases scored for each point = 600.
C = control; E_M = MPG-treated experimental; E_W = WR-2721-treated experimental.
*Mostly asymmetrical types; symmetrical types could not be identified with certainty.
†$p < 0.001$ compared with control
‡$p < 0.01$ compared with control.
NS = Not significant.

DISCUSSION

The present finding that the percentage of aberrant cells increases linearly with exposure dose agrees with the earlier reports of Littlefield and Joiner (1978) and Lloyd et al (1980). The increase in the number of aberrations/100 cells with aberrant-cell frequency supports the earlier observation of Nowell et al (1965). An increase in the complex unstable aberrations with increasing radiation dose has been observed by Dolphin and Lloyd (1974) and Lloyd et al (1980).

Tanaka and Sugahara (1970) observed that MPG protects chromosomes of peripheral lymphocytes from cancer patients undergoing radiotherapy. Our own observations on mouse bone marrow after a single dose of γ radiation indicated that the action of MPG may be at the level of repair rather than at the initial yield of breaks (Uma Devi & Gupta, 1984). The present finding, that MPG is more effective after lower doses of radiation, suggests that it is less efficient in repairing double-strand breaks; an increase in single-strand break repair by the drug has been reported by Modig et al (1977).

The present and earlier findings (Gupta & Uma Devi, 1984) suggest that WR-2721 protects the bone-marrow chromosomes by reducing the number of initial breaks as well as by facilitating the repair process. Radiation-induced double-strand breaks are assumed to be the crucial lesions leading to cell killing, somatic mutations or chromosomal aberrations (Chadwick & Leenhouts, 1983). The present finding, that WR-2721 protects against the complex aberrations after higher radiation doses, indicates its role in facilitating the repair of double-strand breaks. Riklis et al (1983), on the basis of measurement of thymidine incorporation, demonstrated that WR-2721 increased the DNA repair capacity after irradiation. They suggested that this effect of the drug is a result of both radical scavenging, with reduction of damage, as well as increased repair by protection of the repair enzymes. However, this aspect of WR-2721 protection needs further confirmation.

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(The Editors do not hold themselves responsible for opinions expressed by correspondents)

The tissue-rescuing unit

THE EDITOR—SIR,

Recently it has become clear that quantal responses of tissues to irradiation can be described by considering a tissue to be composed of a number, *K*, of death-preventing or tissue-rescuing units (Hendry et al, 1983; Thames et al, 1986). This note presents a definition of the tissue-rescuing unit (TRU) and considers its interpretation on a cellular basis.

The TRU is defined as one of *K* identical units of tissue, each of which is capable, on its own, of rescuing the whole tissue from failure or from a specified level of injury. Hence, using Poisson statistics, the probability of the injury occurring can be described by:

$$p = e^{-KS} \qquad (1)$$

where *S* is the survival probability of each of the *K* TRU in a tissue. This formulation is valid whenever *S* is small and *K* is large.

S is a function of dose and, hence, Equation (1) can be expanded as required, for example, with single doses as:

$$p = e^{-KE \cdot \exp - D/D_0} \qquad (2)$$

$$\text{or } p = e^{-K \cdot \exp -(\alpha D + \beta D^2)} \qquad (3)$$

and for fractionated doses as:

$$p = e^{-K \cdot \exp - [n(\alpha d + \beta d^2)]} \qquad (4)$$

where *E* is the extrapolation number, D_0 is the mean lethal dose for the inactivation of a TRU, α and β are constants in the linear-quadratic formulation which describes the survival of a TRU and *n* is the number of dose fractions of size *d*.

These formulations are useful for quantifying dose–incidence curves for tissue responses. However, the cellular interpretation of the value of *K* and of the sensitivity parameters depends on the composition of the tissue and other factors, as follows.

If each clonogenic cell in a hierarchical tissue containing *N* such cells has an independent probability *a* of rescuing the tissue from failure, then the probability of tissue failure is

$$p = (1 - aS)^N \qquad (5)$$

When *S* is small and *aN* is large

$$p \sim e^{-aNS}.$$

S is the level of cell survival (Lange & Gilbert, 1968). We can define $K = aN$ and, in this case, the TRU comprises a number of clonogenic cells, each contributing independently to the rescue, irrespective of its location in the tissue. By comparing Equations (1) and (5), it may be seen that the sensitivity parameters for the clonogenic cells (*e.g.* D_0 or α and β) are the same as those for the TRU and, thus, determine the slope of the dose–response curves for the tissue. Several examples of this type have been published.

(a) The first test of this hypothesis was performed by Lange and Gilbert (1968), measuring the rescue of planaria by grafted or endogenously surviving neoblasts (planarian stem cells). For diploid planaria of the strain *D. lugubris*, $K \approx 5$. As there were 1.4×10^5 neoblasts in the unirradiated planaria, one TRU comprised approximately 2.8×10^4 neoblasts.

(b) Analysis of the dose–incidence curves for intestinal failure in mice in terms of the survival of crypts (cr) gave $K_{cr} = 1.5$ (Hendry et al, 1983). As there are about 7.5×10^5 crypts per small intestine, this indicates that one TRU comprises 5×10^5 crypts. Furthermore, if there are, for example, about 30 clonogenic cells per crypt (Potten et al, 1986), then in terms of the survival of clonogenic cells (c), $K_c = 45$, and one TRU comprises about 1.5×10^7 clonogenic cells. The validity of the approach in this situation, where each clonogenic cell contributes independently to the rescue of the tissue, was confirmed by the agreement between target-cell D_0 values deduced from the animal mortality data (1.25±0.22 Gy) and colony techniques (1.23±0.08 Gy).

(c) For haemopoietic failure in mice, $K = 10^4$ (Hendry & Moore, 1985). As there are about 10^6 stem cells (CFC-S) per mouse, one TRU should comprise about 100 CFC-S. The D_0 value deduced for the target cells using low dose-rates was 1.14±0.40 Gy (X rays) and 1.15 Gy (γ rays), similar to the values of about 1.0 Gy measured using the spleen colony technique (data reviewed by Hendry and Lord, 1983).

(d) For non-healing of tail epidermis in mice, $K\,\text{cm}^{-2} \approx 450$, and one TRU comprised about nine colony-forming cells in the basal layer (Hendry, 1984). These values were deduced by fitting a common slope ($D_0 = 3.3$ Gy) to the colony data and the data for the healing end-point. The slopes fitted separately to the data gave $D_0 = 3.45 \pm 0.36$ Gy (colony data) and 2.78±0.51 Gy (data for the healing end-point).

(e) Values of *K* were determined for three sizes of tumour spheroid grown in culture (Moore & Hendry, 1984), as shown in Table I. Obviously, the values depend on the size of the spheroid, but interestingly for the smallest (Na11) the content of a TRU was not significantly different from a single cell. In this case every morphologically viable cell could repopulate the spheroid.

The responses of tissues can be analysed using Equations (2)–(5), but in those cases where the structural and proliferative organisation of the tissue is unknown and where colony techniques are unavailable, the interpretation of the parameters is uncertain (Hendry & Moore, 1985, and see below). Two examples are as follows.

(f) For mouse lung, $K = 10^2$ (Hendry & Moore, 1985), a value deduced from data reported by Hornsey et al (1975). The deduced D_0 was 1.5 Gy at a dose of 13 Gy. Much higher values of *K* (4×10^3–27×10^3) were deduced by Thames et al (1986) using new data. More extensive experiments and analyses by Travis and Tucker (1986) produced values for *K* of 10^3–10^5, with a deduced D_0 value for target cells of about 0.6 Gy (range 0.4–0.8 Gy). The number of units, *K*, is of the same order as the number of acini in the animal, and the data indicate that each one could contain 10–10^3 target cells (Travis and Tucker, 1986).

(g) For mouse oesophagus, $K = 10^2$ (Hendry & Moore,

TABLE I

K VALUES REPORTED FOR DIFFERENT TISSUES

Tissue	K (TRU)	TRU content	Reference
Planaria	5.3	2.7×10^4 neoblasts	Lange & Gilbert, 1968
Mouse intestine	1.5 (crypts)	5×10^5 crypts	Hendry et al, 1983
	45 (clonogens)	1.5×10^7 clonogens	
Mouse bone marrow	10^4	100 CFC-S	Hendry & Moore, 1985
Mouse tail epidermis	450 cm^{-2}	9 clonogens	Hendry, 1984
Tumour spheroids			
Nall	232 ± 235	1.6 cells*	Moore & Hendry, 1984
8-day V79	98 ± 29	78 cells*	
21-day V79	350 ± 93	88 cells*	
Mouse lung	10^2	–	Hendry & Moore, 1985
	$(4–27) \times 10^3$	–	Thames et al, 1986
	$10^3–10^5$	$10–10^3$ Type II cells	Travis & Tucker, 1986
Mouse oesophagus	10^2	–	Hendry & Moore, 1985

*Morphologically viable cells.

1985), a value deduced using data reported by Hornsey and Field (1979). The deduced D_0 was 3.4 Gy at a dose of 29 Gy.

In examples (f) and (g), the parameters must be regarded as operational rather than direct reflections of target-cell survival, because colony techniques are not available for assessing cell survival directly *in situ*. Caution is necessary because there is an alternative model to that presented in Equation (1), in which networks of cells are considered. In the extreme case, inactivation of one cell could inactivate the network (this is analogous to the target theory for *cell inactivation* where the inactivation of only *one* target is sufficient to inactivate the cell (Chadwick and Leenhouts, 1973; Gilbert et al, 1980), in contrast to the theory where *all* targets have to be inactivated).

If the tissue consists of N networks, each with M cells which have survival probability S, then the probability of survival of the network (S') is S^M. If each network has an independent probability, a', of rescuing the tissue, then the probability of tissue failure is

$$p = (1 - a'S')^N$$

$$\sim e^{-a'NS'} \text{ if } a'\,S' \ll 1 \text{ and } N \gg 1$$

Hence, $K = a'N$ and $S' = S^M$. In this case the TRU is a number of independent networks of cells, and the sensitivity parameter will be increased by the power M. It should be noted firstly that the increased sensitivity will produce very steep dose–incidence curves and deduced D_0 values which may be uncommonly small. Secondly, the high dose approximation to the multitarget equation is used in Equation (2): if S' is big enough for the full form of the multitarget equation to be appropriate, M will be less than expected for values of p in the common measurable range from 5% to 95% (Hendry, 1985). Thirdly, the network approach also applies between the two extremes considered here (namely, *each* clonogenic cell has rescue potential or alternatively, *all* cells in a network must survive for the network to survive): for example, in the cases where single clonogenic cells have zero rescue probability but two or more together would contribute to rescue, each with a fixed probability (Hendry, 1985), or alternatively, where several of many cells in the network must be inactivated in order to inactivate the network.

In spite of these difficulties of interpretation, the concept of the tissue-rescuing unit is necessary to describe dose-related incidences of effects in tissues, and its continued use and interpretation is encouraged. Values of K reported for different tissues are given in Table I.

Yours, etc.,

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Assessment of the current use of rare-earth screens in the United Kingdom

The Editor—Sir,

I have surveyed the current use of tungstate screens in the United Kingdom by writing to 196 superintendent radiographers. I asked them to estimate the proportion of examinations carried out in their departments with rare-earth screens and their work load in terms of the number of patients examined. I had replies from 172 who were responsible for over 60% of all examinations carried out in the United Kingdom. Forty-eight per cent of the examinations were carried out with "rare-earth screens" and 52% with "tungstate".

The total exposure to man-made ionising radiation in the United Kingdom is estimated to be at an annual rate of 16 000 man.Sv (Hughes & Roberts, 1984). The great majority of this, 14 000 man.Sv, arises from medical procedures. Other major causes include the mining and use of coal (460 man.Sv), fallout from nuclear-weapon testing (615 man.Sv), other occupational exposures (270 man.Sv) and the whole nuclear fuel cycle, including fuel preparation and processing and generation (120 man.Sv). Of the medical exposure, 12 000 man.Sv per year is estimated to arise from conventional diagnostic radiography. This figure could be substantially reduced.

For a given resolution, rare-earth screens allow at least a halving of the dose compared with that delivered using the old tungstate screens (Christensen et al, 1978). Assuming a 50% reduction in dose with rare-earth screens, there is a potential for reducing the conventional dose from radiography in the United Kingdom from 12 000 man.Sv to 9000 man.Sv per year. In addition, the use of carbon fibre material and similar substances in various components in the primary beam (table top, cassette face, grid covers and grid interfaces) allows a further reduction of 40% in the radiation dose to the patient (Hufton & Russell, 1986). These items are in very rare use now and there is, thus, a further potential for reducing the dose to the patients to 5400 man.Sv a year from conventional radiography without reduction in image quality. Other techniques to reduce the patient dose are available, including that arising from fluoroscopy (Berry & Oliver, 1976; Gray & Swee, 1982).

There is, thus, a potential for reducing the United Kingdom exposure from man-made ionising radiation using these techniques from 14 000 man.Sv to under 7000 man.Sv a year. In many other developed countries the radiation dose from diagnostic radiography is two or even four times greater than that in the United Kingdom, with the potential for greater savings.

The cost of reducing radiation exposure using the above methods has been estimated (Russell & Webb, 1985) and varies per man.Sv saved from zero to £300. This should be compared with the minimum of £3000 per man.Sv which the National Radiological Protection Board (1984) have indicated as a value detriment from radiation and as much as £50 000 that British Nuclear Fuels are now spending to avoid a man.Sv. A major effort to introduce these methods of radiation protection into radiodiagnosis should be made.

Yours, etc.,
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Proceedings of Symposium Mammographicum '85

Third Meeting held at Imperial College, London, September 12–13, 1985

Recent Advances in Technique

Chairman: Dr A. K. Tucker

The physics of filters, grids and magnification, by D. R. Dance
The clinical value of K-edge filters, grids and magnification mammography, by J. L. Price

THE PHYSICS OF FILTERS, GRIDS AND MAGNIFICATION

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The choice of photon energy in mammography is a compromise between the requirements of good contrast and low dose. Computations were presented to demonstrate that the use of an X-ray spectrum from a molybdenum target and filtered with a molybdenum filter is appropriate for imaging small to medium breasts. However, for large or very dense breasts the spectrum is far from ideal (Dance & Day, 1981): much of the dose arises from low-energy photons which cannot penetrate the breast and contribute no information to the image. The use of a palladium K-edge filter (Beaman et al, 1983; Bakir et al, 1984) was discussed and its suitability for imaging large breasts demonstrated by calculations of contrast and dose. Dose reductions for a factor of 2 or 3 could be achieved for imaging thick breasts with a tungsten target–palladium filter combination with only a minimal reduction in contrast. Dose reductions of 35% could be achieved with a molybdenum target–palladium filter combination.

The use of antiscatter grids to improve contrast was discussed and detailed computations for a Philips mammographic grid (Dance & Day, 1984) were presented. The contrast enhancement factor for this grid varied between 1.2 and 1.7 for breast thicknesses of 2–8 cm and the corresponding Bucky factor was in the range 1.7–2.2. The dose increase could be offset by the use of a K-edge filter.

Magnification mammography offers the possibility of improved unsharpness and contrast but with an associated dose penalty. The effect of focal-spot size on unsharpness was demonstrated and the importance of using a focal-spot size of 0.1 mm or less was stressed. At this size, a magnification of 1.5 was appropriate and the unsharpness was then improved by 35%. The dose increase could be as high as a factor of 2.7 but, again, could be offset by using a K-edge filter.

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THE CLINICAL VALUE OF K-EDGE FILTERS, GRIDS AND MAGNIFICATION MAMMOGRAPHY

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The prime requirement for mammography is a good, low subject contrast definition so that calcific particles of 100–200 μm can be identified and low-density shadows and areas of architectural disturbance are clearly defined at as low a radiation dose as possible. K-edge filtration of the primary beam can give near-optimum spectral quality and can reduce the radiation dose. The radiation from a tungsten anode tube with 0.05 mm of palladium filtration was found to be suitable (Beaman et al, 1983) and, when compared in clinical practice with radiation from a conventional molybdenum anode tube, was found to reduce the radiation dose by half. This system allows a fine focal spot with greater tube loading and this leads to the possibility of magnification radiography at a reasonable radiation dose. The skin dose was measured using thermoluminescent dosimetry in 28 women for ×1.5 magnification and was found to be in the range 1.2–3.8 mGy. To demonstrate the perceptibility of fine detail with low subject contrast, a perspex phantom similar to a pocket chessboard was devised. Holes were drilled in the centre of the squares, decreasing in size along one axis and in depth along the other. Randomisation was introduced by superimposing slats containing scattered non-uniform holes. This test object gave a convincing demonstration of the improvement in perceptibility using magnification techniques. In a clinical setting, magnification mammography contributed to the surgical management in 17% of 133 cases and was non-contributory in 44%. In the remaining cases, there was some reassurance and confirmation of the initial diagnosis. There was evidence that the biopsy rate was reduced in patients with microcalcification and that cancer diagnosis was enhanced in mammographs with vague densities where architectural disturbance was shown. Unsuspected multifocal cancer was also revealed.

Film definition is degraded by the effect of scattered radiation and grids are effective in reducing this but with a penalty of increased radiation dose. The use of a stationary grid was found to double the skin dose and a moving grid (on Elscint apparatus) increased it by a further factor of 1.4. Fortunately, it has been shown that a worthwhile reduction in radiation dose can be achieved using 0.025 mm palladium filtration with a molybdenum anode (Bakir et al, 1984; Price et al, 1985). A slightly higher kV is used with palladium filters and it was shown that the use of a molybdenum anode–palladium filter combination with a stationary grid produces a dose similar to that obtained using a molybdenum anode–molybdenum filter combination without a grid, but gives the benefit of increased contrast and definition. This would justify the routine use of grids at an acceptable radiation dose.

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Breast Pain

Chairman: Professor R. Blamey

Medical aspects of breast pain, by J. B. Davey
Surgical aspects of breast pain, by P. E. Preece
Radiological aspects of breast pain, by E. J. Roebuck
Pathological aspects of breast pain, by T. J. Anderson

MEDICAL ASPECTS OF BREAST PAIN

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Most women accept breast pain as a "normal" pre-menstrual problem and it has been said that 80% of women with pain never get to hospital for advice. This has been confirmed by a study in Southampton by Nichols et al (1980) The majority of women attending a hospital breast clinic with pain seek reassurance that cancer is not responsible. Few seek medical advice, even when pain is so severe that it upsets their way of life.

Some 24 000 women have been seen in the Early Diagnostic Unit of the Royal Marsden Hospital, the majority having been referred by their general practitioner to exclude breast cancer in the patient with minimal symptoms or a "difficult" breast on clinical examination. One-fifth had breast pain and it was the commonest symptom compared with the surgical out-patient clinic, where a lump is the most frequent symptom.

The clinical syndromes of mastalgia have been reported from the Cardiff Breast Clinic (Preece et al, 1976) and are found to be similar in this series of women. Possible causes of breast pain were detailed and it is noted to occur in the anxious multiparous women rather than the frustrated nulliparous women mentioned in mastalgia patients in previous reports.

Somewhere between 15% and 20% of breast cancer patients present with pain, usually in the premenstrual phase, often pricking in character and unilateral, but it may be cyclical. Of the women with cancers detected in the Early Diagnostic Unit, 17% had pain with a lump being present, but when no lump was present the proportion was increased to 25%.

The multiplicity of therapy prescribed for "benign" breast symptoms such as pain suggests that few drugs are specific. The hormonal influence is complex and variable, making individual treatment difficult to manage. Mention of common drug therapy was made, but many patients should be managed by reassurance alone judging by the quick response to simple treatment following a normal clinical and mammogram examination.

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SURGICAL ASPECTS OF BREAST PAIN

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Pain is the commonest complaint related to the female breast, both in general practice and in clinics. In the past, the symptom has not elicited much serious study from clinicians. It has not been regarded as indicative of disease. Like pain anywhere, the significance of pain in the breast to the woman experiencing it is difficult to measure.

A history enquiring about all the usual parameters of pain, wherever this is felt, goes some way to understanding the problem for the individual. Contributing most to this is the distinction between cyclical and non-cyclical pain. Cyclical mastalgia is a problem because it is either prolonged or pronounced. It has several distinctive characteristics. It is not suggestive of life-threatening disease, but it can seriously disrupt the life of the patient.

Non-cyclical mastalgia may be caused by pain radiating to the breast from disease elsewhere, such as gallbladder, lung, myocardium or spine If it arises within the breast, the cause may be either benign or malignant. Benign causes of non-cyclical mastalgia include biopsies, fat necrosis, periductal mastitis and sclerosing adenosis. Early cancer of the breast can be identified at a painful locus, or within a breast where pain has been present. Lobular carcinoma is particularly associated with mastalgia as an early, and sometimes as the sole, symptom.

Although there are important surgical considerations relating to pain in the breast, especially those bearing on surgical technique, ablative surgery is rarely successful as a treatment for intractable idiopathic mastalgia.

THE RADIOLOGICAL ASPECTS OF BREAST PAIN

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There are radiographic difficulties which must be overcome before radiological problems can be adequately elucidated. Most of these relate to the difficulty of obtaining the degree of breast compression which is essential to adequate image quality. Where possible, mammography should be performed at the least painful time in the cycle and pain-minimising preparation, such as the avoidance of caffeine, may also be of value. The difficulty in compression may, in turn, give rise to poor positioning.

Localised breast pain is likely to be of greater significance if there is an associated clinical abnormality and radiology should be directed to the elucidation of the cause. If none can be found, the suspicion of an occult cancer remains.

Pain may be associated with parenchymal or periareolar mammographic abnormalities and, in either case, comparison with the contralateral side is required. The most common localised parenchymal abnormality is an ill-defined area of density, which may be due to dysplastic activity, or may obscure a benign or malignant lesion. Secondary investigation by ultrasound is of great value and will reduce the number of follow-up examinations. A leash of prominent duct shadows extending into a segment (a "P" reaction) may be a very significant pointer to a carcinoma. Prominent duct shadows close to the areola are due to duct ectasia rather than an increase in periductal shadowing. Inflammation in duct ectasia is a common cause of pain and gives rise to mammographic asymmetry associated with an appearance of oedema. To confirm this interpretation by ultrasound so close to the areola is difficult and, since an identical appearance can be associated with a carcinoma, cytological examination or follow-up is desirable.

Management decisions are assisted by the presence of multiduct discharge, likely to indicate inflammation, or single-duct discharge, when a microductectomy may reveal a benign or malignant lesion.

If unilateral periareolar pain is not accompanied by any mammographic asymmetry, the existence of a carcinoma should be strongly suspected and follow-up is mandatory unless a secondary investigation (cytology or ultrasound) elucidates the cause of pain.

PATHOLOGICAL ASPECTS OF BREAST PAIN

T. J. Anderson

University of Edinburgh

Two aspects to consider are the microanatomical explanations for the symptom of breast pain and the disease processes or tissue alterations that may be associated with it. Although different types of sensory nerve endings have been noted in the deeper elements of the breast, knowledge of the innervation of the internal parenchymal structures is poorly documented and there is no standard pattern. Much of the cyclical mastalgia is considered physiological and a contributory factor is the fluctuation in mucopolysaccharide composition of the stromal ground substance of breast lobules in response to hormones. Inflammation is infrequently of acute pyogenic type, with chronic periductal mastitis a much commoner feature accounting for localised pain. The usual end-stage of this process is duct ectasia. Trauma of whatever type is painful and may also provoke an inflammatory process that will be associated with fat necrosis.

Breast structural alterations with benign or malignant characteristics have both been associated with the symptom of pain, but lesions with these features are more commonly painless. Benign sclerosing processes have been associated with mastalgia and these result in a spectrum of changes that may cause difficulties in mammographic interpretation and distinction from malignancy. Fine-needle aspiration cytology now offers a minimally invasive means to evaluate such painful lesions. Malignant and suspicious reports will identify those requiring rapid surgical investigation. Correlation of the pathologists' findings with those of physical examination and mammography provides the optimum combination of modalities by which to manage the other cases with repeat procedures as necessary.

Panel Discussion of Cases

Chairman: Dr C. A. Parsons

Panel: Professor R. W. Blamey, Queen's Medical Centre, Nottingham
Dr A. K. Tucker, St Bartholomew's Hospital, London EC1
Dr A. E. Kirkpatrick, Royal Infirmary, Edinburgh

Alternative Methods of Investigation

Chairman: Dr E. J. Roebuck

Spectrascan Litescanning, by A. K. Tucker
Magnetic resonance imaging (1), by J. T. Ennis
Magnetic resonance imaging (2), by L. te Strake, W. R. Obermann, C. J. H. van der Velde, H. Pieterman and J. Doornbos
Direct-contact B-scan sonomammography (breast ultrasound), by P. B. Guyer
Prediction of high-risk benign breast disease by immunohistochemistry, by R. E. Mansel
Breast aspiration cytodiagnosis, by P. A. Trott

SPECTRASCAN LITESCANNING

A. K. Tucker

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Transillumination is an imaging technique used to diagnose breast cancer. A trial was done to test the accuracy of the Spectrascan transillumination system against mammography, which at present is the most accurate method of detecting early breast cancer. The Spectrascan uses pulsed near infra-red and visible light from a narrow beam source. The transmitted light is recorded by video camera and displayed on a monitor; the differential absorption is processed by computer and colour coded and then finally recorded on disc and on tape. The mammography was standard practice for our centre, using a Siemens Mammomat B machine, with Kodak Ortho M film and Min R screens.

A series of 540 women was reviewed by both techniques in a blind trial with both modalities reviewed by the same person, but at different times and in a different sequence to ensure unprejudiced assessment. Of the 540 women, most were well-women screening patients but, in order to increase the number of possible cancers, some direct-referral patients were included.

Of the eight histologically proven cancers, seven were positive on mammography and one was equivocal. Four were positive on Spectrascan, including the case which was equivocal on mammography, two were equivocal and two were missed. Of 13 other possible cancers (histology results not yet received), nine were positive on mammography and two were equivocal. Eleven were positive on Spectrascan and two were equivocal.

In benign lesions many more cysts were found by Spectrascan. For patient preference, 13.1% preferred Spectrascan, 2.2% preferred mammography, 28% had no preference and 57% failed to fill in the form.

The conclusion from this limited trial is that Spectrascan does pick up cancers and is without the hazards of ionising radiation. It is not as accurate as mammography, but allowance must be made for our limited experience of Spectrascan compared with our considerable experience in mammography. Both technique and interpretation require great care, as does mammography, but Spectrascan takes longer than mammography to perform. Spectrascan would be very useful in the young dense breast where irradiation was contraindicated and particularly in the presence of breast prostheses, which obscure detail. In repeated follow-up Spectrascan has the great advantage of not involving ionising radiation.

MAGNETIC RESONANCE IMAGING (1)

J. T. Ennis

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With the advent of specially designed surface coils, magnetic resonance imaging (MRI) provides diagnostic information on breast pathology without the use of ionising radiation. Volume thin-sliced images can be obtained at 5 mm intervals in coronal, axial and saggital planes. The imaging time is approximately 8 min. The anatomical detail allows one to identify the ductal tissue, the retromammary fibrous tissue and the axilla clearly.

Twenty-five normal volunteers who had normal xeromammograms were examined using a specially made surface coil and spin-echo volume slices. The anatomical detail for MRI was superior to xeromammography and the ability to demonstrate the pectoralis muscle was a decided advantage. Using the parenchymal classification of Wolfe, MRI clearly defined the ductal structures and, using three-dimensional images, was more accurate in quantifying the residue of ductal tissue.

Ten abnormal patients were examined and MRI clearly demonstrated the abnormality in all patients. Lesions as small as 5 mm were seen and, on the routine images, carcinomas were shown to have irregular margins with long T_2 sequences. Extension of the cancer to invade the pectoralis muscle was superiorly demonstrated in one patient.

In conclusion, MRI is a new method which offers no radiological hazard to the patient but can detect lesions at the 5 mm stage. It remains to be seen from quantification (T_1/T_2 indicates and *in-vivo* spectroscopy) whether this method will be superior in selected patients. The use of ferro-magnetic contrast agents also requires evaluation.

MAGNETIC RESONANCE IMAGING (2)

L. te Strake, W. R. Obermann, C. J. H. van der Velde,
H. Pieterman and J. Doornbos

University Hospital, Leiden, The Netherlands

The limitations of current imaging modalities justify a study with the objective of evaluating the potential role of magnetic resonance imaging (MRI) in the diagnosis of breast disease. The limitations of X-ray mammography include the use of ionising radiation, the detection of a lesion in the dense breast and the differentiation between a benign and malignant mass. With ultrasound, microcalcifications remain undetected, a small carcinoma in the fatty breast may be missed and accurate differentiation between a benign and a malignant solid mass is not always possible.

Twenty-nine patients suffering from both benign and malignant conditions were studied with the 0.5 T superconducting Gyroscan S5 (Philips). Two types of surface coils were used as a receiver: a commercially available coil for the examination of the patient in the prone position and a more flexible system designed in our department of radiology, allowing the examination in the more comfortable supine position with a coil that can be adapted to the size of the patient. Cysts, being of higher signal intensity (SI) than fat on heavily T_2-weighted images, can be differentiated from solid lesions. A carcinoma may be recognised by its irregular contour. Increased SI of the carcinoma on T_2-weighted images (El Yousef et al, 1985; Von Heywang et al, 1985) was observed in only two of the eight carcinomas. Microcalcifications, present in five of eight carcinomas, could not be detected. The detection of a small fibroadenoma in a dense breast proved to be difficult.

Advantages of MRI are its ability to image the entire breast, including the axillary tail, and the non-use of ionising radiation. However, high cost, long examination time, lack of specificity due to overlap of the T_1 and T_2 values for benign and malignant tissue and the failure to detect microcalcifications are important factors that, at this stage, will hamper the acceptance of MRI as a clinical tool, particularly as a screening procedure, in the diagnosis of breast disease. The method is rapidly developing and needs further evaluation. Future developments, particularly magnetic resonance spectroscopy, may add to the specificity of nuclear magnetic resonance and its clinical usefulness.

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DIRECT-CONTACT B-SCAN SONOMAMMOGRAPHY (BREAST ULTRASOUND)

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X-ray mammography using a Senograph and a Kodak Min R film-screen combination revealed 87% of carcinomas present; 8% were obscured by breast density and 4% were interpreted as benign. Ultrasound was introduced to improve the diagnostic accuracy; 2000 patients have been examined, of whom 1333 have had X-ray mammography. Of 288 proven carcinomas, 287 were detected sonographically, but 20 (7%) were misinterpreted as benign (16 as fibroadenomas); only one was not detected (shown radiologically as a microcalcification). X-ray and sonomammography were equally informative in 161 of 260 patients undergoing both investigations. In 72 patients ultrasound was superior, identifying carcinoma in 34 of these with increased X-ray density, and being more certain of malignancy in the remaining 38. In 12 patients radiology was superior due to microcalcifications or striations; 14 out of 20 ultrasound misinterpretations had both investigations and in two of these radiology indicated malignancy.

Of the 287 carcinomas imaged by ultrasound, 113 showed a hypoechoic nidus, a "halo" of bright echoes and distal attenuation ("shadow"); 48 showed a mass alone and included most misinterpretations; 56 showed attenuation only and the others showed varying combinations of these features.

In 1722 patients with benign breast disease, ultrasound was more informative than radiology in 50%, revealing cysts, fibroadenomas, or fibroadenosis in X-ray density. There were 88 fibroadenomas; most were well defined, hypoechoic masses without the "halo" and "shadow" of carcinoma. Of 203 consecutive patients referred with a breast lump, 71 with benign breast disease were scheduled for biopsy, which was averted in 22 when ultrasound failed to show a mass and in four when cysts were aspirated during sonomammography, after aspiration failed in the outpatient department; five examinations showed unsuspected malignancy.

We use sonomammography as the primary investigation in patients under 35 years of age with clinical benign breast disease, followed by radiology when malignancy is revealed. Sonomammography is also used after radiology for clinical lumps. It is a procedure which needs more radiologists' time and its insensitivity to microcalcifications makes it unsuitable for screening.

PREDICTION OF HIGH-RISK BENIGN BREAST DISEASE BY IMMUNOHISTOCHEMISTRY

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Current methods of risk estimation for breast cancer are mostly of weak predictive value. Personal endocrine factors such as age at first pregnancy are statistically significant but of little value in clinical terms. Family history can be useful if it occurs in a first-degree relative who has pre-menopausal breast cancer.

Recent studies of the value of histological changes on a benign breast biopsy show a clear correlation with hyperplastic ductal or lobular epithelium when atypical changes are also present. The predictive value of atypical hyperplasia is increased if the patient also has a positive family history (Dupont & Page, 1985). However, accurate reading of atypical changes is difficult and the terminology varies from pathologist to pathologist. The use of monoclonal antibody immunohistochemistry allows the detection of cancer-related antigens in non-cancerous breast tissues. Many epithelial membrane antigens have been identified using this method but most of them are present on both benign and malignant breast cells. Some antigens, however, appear to be restricted to malignant or pre-malignant tissues and these may be of some value in estimation of cancer risk from immunohistochemical slides. An antibody, which stains most cancers but only 10% of benign breast disease samples, is currently under study to find out whether it will be of value in risk estimation. Slide reading is easy using the immunoperoxidase technique and paraffin-embedded tissue can be studied.

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BREAST ASPIRATION CYTODIAGNOSIS

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In the United Kingdom during the last 10 years there has been a very rapid expansion in the use of the technique of breast aspiration cytodiagnosis. This has come about as a result of many factors, of which the most important is the awareness by doctors and patients that radical surgery is not necessarily the best treatment and therapy should be "tailored" to individual patients; hence, a need for pre-operative diagnosis. In the modern surgical outpatient clinic the combination of clinical examination, mammography and biopsy separates women with benign and malignant breast lesions so that a patient with a carcinoma can be investigated for metastases and advised about treatment. In an analysis, at the Royal Marsden Hospital, of 77 patients with carcinoma, all except one were diagnosed using at least one of these three methods and in five patients positive needle aspiration cytology was the only abnormality (Thomas et al, 1978).

The practice of pre-operative diagnosis varies in different clinics and, in some hospitals, biopsy is performed using a wide-bore Trucut needle and sent for histopathological examination. This technique has the advantage of a higher accuracy of diagnosis because more tissue is removed than with a narrow needle but is rather painful, especially when benign, rather indistinct lesions are biopsied. Aspiration using a narrow, 22-gauge needle is less uncomfortable and can, therefore, be repeated if an unexpected result is obtained. Indeed, many of our patients have several aspirates from both breasts and, occasionally, from axillary nodes as well.

The tissue is smeared on a slide and either fixed immediately in an alcoholic solution or air dried and stained similarly to a blood film. In about three quarters of the carcinoma cases the diagnosis is obvious and the large, pleomorphic, irregular cells reveal the nature of the mass. In a smaller number of cases experience in cytodiagnosis is needed to distinguish well differentiated carcinomas from florid fibroadenomas and a cellular fibroadenoma from carcinoma.

Recent research has shown that the oestrogen receptor status can be established satisfactorily from aspirated tissue using immunocytochemistry so that appropriate hormone or endocrine treatment can be given.

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Radiographic Topics

Chairman: Dr J. B. Davey

How to train radiographers, by J. Taylor
Additional views, by M. Yeowell
Roles of the radiographer in a mammography service, by J. Tew
Important clinical signs, by B. A. Thomas

HOW TO TRAIN RADIOGRAPHERS

J. Taylor

Xerox Medical Systems International, Hayes, Middlesex

The detection of breast cancer requires a team effort and one of the most important members of that team is the radiographer. Mammography is one of the most difficult examinations in radiology to interpret. Therefore, without proper motivation and training, a poor mammography service will be offered.

One of the most important factors to be discussed before any training can take place is the type of person to be trained. Essentially, it must be a female who has empathy with the patient, is mature in outlook, diligent in her work and above all else, it must be someone who wants to do mammography. Ideally the training period should be divided into two separate sections, theory and practical, with the theoretical work being done before the radiographer encounters her first mammography patient, thus ensuring that she presents a confident and professional attitude towards the patient. Training should cover the anatomy of the breast, a full understanding of the imaging process involved, how to take patient history, to position and compress the breast, and to mark the image correctly. It should also give a basic understanding of the pathology involved. An often neglected area of training is that of teaching the radiographer to assess the quality of her own work.

Most importantly, it is my firm belief that if a radiographer does not wish to do mammography she should not do it as the quality of work will never be of the required standard, and indeed, wherever feasible, specialist mammographers should undertake the examination.

ADDITIONAL VIEWS

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Cranio-caudal and lateral views are generally accepted for mammography. The 45° lateral oblique view demonstrates the maximum amount of breast, axillary tail and axillary nodes, and should replace the true lateral view when there is no clinical abnormality. These routine views are supplemented when necessary by two additional views, the extended cranio-caudal view and the true lateral. The true lateral view will be needed for accurate localisation of clinical and radiologically demonstrated masses. The extended cranio-caudal view will demonstrate much more of the upper outer quadrant and the axillary tail. This area is not always demonstrated on the routine views due to the curvature of the rib cage.

The medio-lateral view gives the most accurate localisation for lesions, not only because it produces a film at exactly 90° to the cranio-caudal view, but because it demonstrates the maximum amount of breast on a lateral view. With the latero-medial and oblique views, the same lesion may appear to be in different positions due to the rotation of the breast. The information provided by these additional views could be vital to confirm or exclude carcinoma.

Mammograms of the highest quality are essential. Radiographers should be encouraged to study films carefully and to ensure that the site of clinical findings is demonstrated and that any pathology is shown in two views. Well exposed films are necessary to avoid missing microcalcification and care must be taken to ensure that artefacts on films do not simulate pathology.

A Siemens Mammomat B machine, with a grid and foot-controlled compression and automatic exposure timer, is used at the BUPA Medical Centre, in conjunction with Kodak Min R cassettes and Ortho MA film, and a longer development cycle in order to produce maximum detail and information.

ROLES OF THE RADIOGRAPHER IN A MAMMOGRAPHY SERVICE

J. Tew

Nottingham General Hospital

A dedicated mammography system is essential for the production of high quality images. This system will include an X-ray unit, a film/screen combination, a film processor and viewing conditions. Choice of these items is governed by the service provided, but for the maintenance of high image quality, a quality assurance programme is necessary to provide the optimum contrast and resolution needed for mammographic interpretation.

A woman with a breast lump presenting for X-ray examination is a very nervous patient. To overcome this and provide a greater clinical understanding of the presenting problem, a simple questionnaire is completed by the radiographer during a short conversation with the patient. This opportunity to discuss not only her symptoms but the examination to follow relaxes the patient and aids patient/radiographer co-operation.

In Nottingham the radiographers are trained by surgeons from the breast clinic to undertake clinical examination of the breast. This extra information enables the X-ray examination to be expanded to take in any further views necessary to include the lesion for radiological diagnosis. Training from interpretation is initially undertaken by an experienced member of the team. Our on-going tuition is gained at weekly meetings with the radiologist to discuss case reports and pathology results. The radiographer records the normal and abnormal signs on a proforma. The final entry is an opinion as to the lesion being benign or malignant.

Using a series of 1307 consecutive symptomatic cases, the radiographers' recommendations were studied with the radiological report. It was found that by referring the follow-up and biopsy recommendations of the radiographer (63%) to the radiologist for report, there would be no detriment to patient management in the remainder of the series, hopefully providing cost-effective primary screening for the early detection of breast cancer, but certainly maintaining very high technical standards.

IMPORTANT CLINICAL SIGNS

B. A. Thomas

Guildford Breast Screening Project, Jarvis Screening Centre, Guildford

We are now entering a new phase in the diagnosis and management of breast cancer. Mammography is the most sensitive technique presently in use for the diagnosis of early disease and the sole screening modality in the successful Swedish Screening Programme (Tabar et al, 1985). Cancers diagnosed when the primary lesion is under 2 cm in diameter with the nodes not involved have an excellent prognosis with over 80% well after 10 years. An increased proportion of such cancers almost certainly accounts for the success of the Swedish Programme. In the absence of a population screening programme an evaluation of clinical diagnostic criteria is mandatory, since many such early cancers have ill-defined symptoms and signs which could, if high quality mammography were available to symptomatic women, lead to diagnosis before the classical signs were apparent

An appraisal was made of symptoms and clinical signs, if any, associated with the 232 cancers 2 cm and less in diameter (as measured by the pathologist) diagnosed between January 1979 and December 1984 in the population registered in the Guildford Breast Screening Project The women are between 45 and 70 years old and are screened annually by clinical examination and biennially by single 45° oblique-view mammography (Thomas et al, 1984). Of these women, 78 had relevant symptoms (34%), of whom 54 thought that they had noticed a palpable change, however indefinite; 22 complained of a localised sensation change, pain or discomfort, and this was the sole symptom in 14; nine noticed a shape change (sole symptom in six) and three had the sole symptom of a nipple discharge. Clinical examination methods need to take account of the very minor changes which may be noted in such women (Thomas, 1985).

A discrete mass was present in only 105 of the 232 cases, even after review with palpation after mammography, and in 18 of these women the lump felt was typically benign. A localised consistency change was found in a further 67 cases, and a localised minor shape change could be elicited by pectoral muscle contraction in 82 cases. These visible signs were illustrated. Of the cases detected by clinical and mammographic screening, repeated clinical examination subsequent to viewing the mammograms increased the clinical abnormality rate by 50%.

Prior to any possible screening programme the provision of high quality mammography for all possible symptomatic women is essential to determine which few women among the many with minimal symptoms and signs actually have early cancer.

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Miscellaneous Topics

Chairman: Dr D. R. Dance

Which unit for which examination? by L. Harris and C. P. Lawinski

Patterns of axillary lymphadenopathy· implications for the asymptomatic woman in a screening programme, by J V Hunter, G J. Hunter and A. K Tucker

Unusual malignant tumours of the breast, by T. S. Brown

Training radiographers to screen mammograms, by B B. Muir, F. Alexander, L. Milne, J. Docherty and M. Roberts

Medico-legal responsibilities in a screening programme, by J. Pemberton

WHICH UNIT FOR WHICH EXAMINATION?

L. Harris and C. P. Lawinski

KCARE, King's College Hospital, London

Part 1. Three mammographic units from three manufacturers were assessed clinically at KCARE, the Jarvis Screening Centre, Guildford and the Queen's Medical Centre, Nottingham. This wide-based assessment has provided an evaluation of the various features of the units in relation to the particular situations at each centre. A price comparison was made of units including accessories. The generators and X-ray tubes were compared and the clinical implications of various features discussed. The designs of the three machines were compared with reference to their practical implications. The diagnostic image quality was reported and the suitability of the machines to the various departments discussed.

Part 2. The three mammography units were assessed for technical performance at KCARE. A brief description of the three systems was given in terms of generator and tube type, target material, filtration, focus–film distance and clinical features. The importance of the X-ray spectrum at mammographic energies was discussed and a system for its measurement described. A number of recorded spectra were shown and related to the clinical performance of each system. The methods for testing the performance characteristics of each generator were described and a summary of the results given, including a comparison of kV calibration and radiation output A brief description was also given of the automatic exposure control systems and secondary radiation grid systems provided.

PATTERNS OF AXILLARY LYMPHADENOPATHY: IMPLICATIONS FOR THE ASYMPTOMATIC WOMAN IN A SCREENING PROGRAMME

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Carcinoma of the breast is the commonest cause of mortality due to malignancy in women in England and Wales. Since early diagnosis offers the best hope for a cure, screening in the form of mammography, with or without clinical examination, is being increasingly used to detect lesions at an earlier stage. Several screening programmes have been established in Europe and the results from some of these have been published (Gad et al, 1984). One centre has claimed that an asymptomatic woman, with axillary lymph nodes present on mammography and no demonstrable underlying carcinoma, has a greater than two-fold increased risk of developing subsequent ipsilateral breast cancer when compared with a woman without demonstrable lymph nodes (Rombach, 1980). If this statement proved to be true, the frequency of subsequent mammography might have to be increased in order to detect the interval carcinoma at an earlier stage. This would have serious implications in terms of the overall resources available for screening programmes. In order to test this claim, a retrospective analysis was performed on the mammograms of approximately 40 000 screened patients using a cluster sampling technique. A group of women with histologically proven breast carcinoma and two control groups were analysed. The incidence, site and pattern of axillary lymph nodes were compared between the three groups. No difference was demonstrated in the incidence of lymphadenopathy (46.3% in controls, 50% in the cancer group). The risk of an asymptomatic woman with axillary lymph nodes developing ipsilateral breast cancer was no different from that of an asymptomatic woman without axillary lymph nodes (relative risk 1.0003). These figures do not support the claim made by Rombach. We conclude, from our study, that the presence or absence of lymph nodes should not form part of the decision pathway used during the assessment of screening mammograms for the early detection of breast cancer.

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UNUSUAL MALIGNANT TUMOURS OF THE BREAST

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Metastatic tumours of the breast have been recorded in the surgical literature (Sandison, 1959). Millis et al (1976) have described the radiology of some uncommon malignant neoplasms. This paper describes the radiology of a small series of patients with malignant disease who presented with breast lumps. Of these, two patients with lymphomatous masses presented *de novo*, the remainder had known malignancy.

No characteristic xeromammographic patterns could be recognised in this series, other than to call masses malignant; if the clinical diagnosis was known beforehand, then a confident tissue diagnosis could be assumed. Of the two patients with lymphomatous involvement, both presented with discrete, intramammary masses, one characteristic of a carcinoma and the other characteristic of intramammary lymph nodes. A further patient with nodular sclerosing Hodgkin's disease developed gynaecomastia. Of three patients with acute myeloid leukaemia, one presented with a tender mass in the right breast, radiologically shown as an ill-defined mass which, on needle biopsy, proved to be a leukaemic deposit. This responded to therapy. A middle-aged Asian male developed bilateral breast lumps probably due to gynaecomastia, but he refused further investigation. Another patient with acute myeloid leukaemia also developed gynaecomastia. An elderly female patient with a previous history of bladder carcinoma developed a mass in the left breast radiographically characteristic of a scirrhous carcinoma which on biopsy showed the same histology as the original bladder tumour. The histopathologist may be very dependent on the knowledge of the clinical diagnosis, as there is a tendency to diagnose unusual breast tumours as anaplastic carcinomas. Similarly many unusual malignant breast masses have appearances characteristic of a carcinoma, and, unless additional clinical information is available, this is the radiological diagnosis which will be offered.

Radiology can discriminate between probably benign and malignant breast lesions, but even some lymphomas will appear as well circumscribed, slightly lobulated masses characteristic of a benign lesion (Millis et al, 1976).

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TRAINING RADIOGRAPHERS TO SCREEN MAMMOGRAMS

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Pressure from the media and lay organisations may lead to demands for breast cancer screening clinics on a countrywide scale before the medical profession is prepared. Such clinics would not only be expensive to run; at present they would be impossible to staff. One means of reducing costs and of providing personnel is to utilise radiographers, not only to take, but also to screen mammograms. This idea is not new (George et al, 1980). In Utrecht, radiographers screen all mammograms (Rombach, 1980).

We have trained two of our radiographers to read mammograms. The initial training period consisted of twice weekly sessions for three months, where they reviewed mammograms of gradually increasing difficulty. Previously diagnosed cancers were reviewed and they attended meetings where newly diagnosed cancers were discussed. After they had read 500 sets of mammograms under close supervision, they entered a more realistic screening situation, although for the purpose of this study, their performance has been compared with that of the clinic doctors who continued to screen mammograms as usual. None of the screeners received any clinical information.

Performance has been assessed after 1050 sets of mammograms have been read. A mammographic lesion was deemed to be present if confirmed at the internal review clinic. In 13 cases, biopsy was recommended (four cancers plus two very suspicious cases proved to be benign) and 19 cases had mammographic lesions not requiring biopsy. The radiographers referred 35% of films for second opinion, compared with 12.5% by the doctors. Sensitivity for confirmed lesions is 94% for the radiographers and 87.5% for the doctors. Specificity for the radiographers is 67% and for the doctors 90%. One small cancer was overlooked by both radiographers. Nevertheless, radiographers could be usefully employed in the initial screening of mammograms, thus reducing the requirement for trained doctors and radiologists. However, they would need the continuous support of a radiologist, with strict attention to quality control.

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MEDICO-LEGAL RESPONSIBILITIES IN A SCREENING PROGRAMME

J. Pemberton

St Thomas' Hospital, London SE1

Screening is the testing of apparently unaffected volunteers to categorise them into those who are likely and those who are unlikely to have the disease in question. It is essential that a screening programme is adequately funded so that the equipment and radiological, radiographic and nursing personnel are of the highest standard. Training must be such that there is consistency of both report and opinion at different centres Inferior quality service is positively dangerous with unnecessarily high biopsy and follow-up rates. This in turn leads to patient anxiety, excess expenditure and often false reassurance.

Over the last decade a lack of an adequate number of radiologists has lead to an increased delegation of responsibility to our radiographic colleagues. This delegation has been particularly pronounced in the field of ultrasound and it has been suggested that this extension of radiographic responsibility might arguably be extended to the reporting of mammograms It is therefore appropriate at this time to examine the legal implications inherent upon this expansion of the radiographer's role.

The General Medical Council's advice on delegation of medical duties reads as follows. "The Council recognises and welcomes the growing contribution made to health care by nurses and other persons who have been trained to perform specialised functions, and it has no desire either to restrain the delegation to such persons of treatment or procedure falling within the proper scope of their skills or to hamper the training of medical and other health students. But a doctor who delegates treatment or other procedures must be satisfied that the person to whom they are delegated is competent to carry them out It is also important that the doctor should retain ultimate responsibility . . ."

The Joint Co-ordinating Committee of the Defence Union holds that the radiologist or other consultant has overall clinical responsibility which includes responsibility for the appropriate instruction and supervision of the radiographers; he or she is, through his or her defence society, liable for acts and omission in respect of clinical work and supervisory functions. The employing authority is responsible for the provision of adequate staffing, the equipment and premises. It has a vicarious liability for the acts incurred by virtue of delegation.

The radiographer, on the other hand, may, with the agreement of his or her employing authority, conduct such examinations and issue such reports as are consistent with his or her experience and qualification. If radiographers are to provide interpretation of mammograms, then it is important to confirm with the Health Authority acceptance of this additional responsibility as a proper part of the duties of their employment. Detailed guidance on these several points should, I feel, be reassessed by the Royal College and by the Society of Radiographers.

Screening for Breast Cancer

Chairman: Dr J. Pemberton

Referrals from screening to surgery, by G. H. Whitehouse
Should we screen the well, investigate the symptomatic or just wait and see? by J. Croll
Periodic screening with one-view mammography: the effect of mortality from breast cancer in a randomised, controlled trial, by L. Tabar, A. Gad, L. Homberg and U. Ljungquist

REFERRALS FROM SCREENING TO SURGERY

G. H. Whitehouse

University of Liverpool

An analysis was made of cases referred from a well-woman Breast Screening Unit to a specialised surgical clinic, with subsequent management and biopsy findings. This experience is based on 10000 examinations. Almost 5% of attendants were referred to the Breast Clinic. The biopsy rate was 20 per 1000 and the carcinoma detection rate 4 1 per 1000.

Rounded, well defined masses were followed up by mammography and/or ultrasound in 47 of 101 cases Thirty-seven cysts were aspirated. Twelve solid masses were all benign on biopsy.

Of the rounded masses with an incompletely defined border, 27 were found to be benign on biopsy and one invasive carcinoma was found. Of 42 cases in whom generally ill-defined masses were found, a third were shown to be carcinomas. Spiculated margins indicated malignancy except for one case of infiltrative epitheliosis. For cases where microcalcification was the only abnormality, aggregations of four or more foci, or irregular forms, were biopsied while the rest were followed up by mammography. Sixteen of 105 biopsies showed carcinoma, two thirds being non-invasive. Sclerosing adenosis was the commonest benign finding. Architectural distortion or spiculation indicated carcinoma, except for one infiltrating epitheliosis with spiculation alone. Asymmetrical dysplasia gave no evidence of carcinoma on follow-up in the 11 cases. Localised duct dilation showed fibrocystic disease in biopsied cases, while others were eventually considered to be plasma cell mastitis.

Of the 41 carcinomas, three quarters were impalpable and 15 were intraductal in situation. The mean age was 50.35 years (range 39–61 years). A mass lesion, with totally or partly ill-defined border, was the commonest appearance of carcinoma. Carcinoma was found in 15% of cases biopsied for microcalcification alone. Thirty-five cases occurred in the Wolfe "high risk" parenchymal patterns The breasts of all women were examined by a trained nurse, but no cancer was found by the nurse when the mammogram was negative.

SHOULD WE SCREEN THE WELL, INVESTIGATE THE SYMPTOMATIC OR JUST WAIT AND SEE?

J. Croll

Sydney Square Diagnostic Breast Clinic (SSDBC), Sydney, Australia

Tabar et al (1985) have reported that high quality mammography, when interpreted by dedicated mammographers, reduced breast cancer mortality in a screened group when compared with unscreened controls. One cannot assume, however, that the mortality reduction would necessarily occur when mammography is performed in less specialised circumstances. In order to reinforce the value of mammographic screening, three Australian populations with invasive duct carcinoma (IDC) of known size and nodal status have been compared.

The screening group comprised 128 consecutive cases of IDC detected in well women screened by film mammography at the Medicheck Referral Centre, Sydney. The investigated group comprised 195 consecutive cases of IDC diagnosed in symptomatic women by aggressive investigation with two or more of the following tests: clinical examination, film mammography, water-bath ultrasonography and fine-needle aspiration biopsy (FNAB) at the SSDBC. The wait-and-see group comprised 434 consecutive cases of IDC reported by Bonett et al (1983) in South Australia, where mammography is an occasional and poorly performed test. There is a statistically significant difference between the number of cancers less than 2 cm in diameter in the screened vs investigate group vs wait-and-see group. Conversely there are significantly more tumours measuring 4 cm or more in diameter and more patients with four or more nodes involved in the wait-and-see population than in the others. However, the screened population had more women with negative nodes than either of the other groups. If nodes negative is agreed to be an index of curability, the screened population has survival advantages over the investigated and wait-and-see groups.

Screening by clinical examination or BSE gives non-specific results, and public money should not be diverted to promotion of these tests. While we wait for proven life-saving mammography screening to be approved by the decision-makers in our countries, we must compromise. Firstly, baseline mammography is desirable at age 40 years or earlier if family history is positive. Secondly, aggressive investigation is necessary in women with persistent unilateral symptoms. Clinical opinion plus mammography will confirm or deny the presence of carcinoma in the majority. However, the author has reported (Croll, 1983) a 20% false negative mammography rate in women under 50 years old with palpable breast cancer. In these cases and in all equivocal cases, water-bath or real-time sonography and FNAB gave valuable added information. In symptomatic women, such investigations lead to a 99% true positive clinical opinion in patients with breast cancer and a 3% false positive rate in patients without breast cancer.

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PERIODIC SCREENING WITH ONE-VIEW MAMMOGRAPHY: THE EFFECT OF MORTALITY FROM BREAST CANCER IN A RANDOMISED, CONTROLLED TRIAL

L. Tabar, A. Gad, L. Homberg and U. Ljungquist

Falun Central Hospital, Sweden

The results from the randomised controlled trial in New York in the 1960s (HIP-study) provided strong evidence that the course of breast cancer can be altered by detecting and treating it at an earlier stage. Encouraged by these results, additional randomised controlled trials have started in Sweden, Great Britain and Canada, in order to find out the effect of screening in different countries and the effect of different screening designs. Those controlled trials which will be evaluated in the coming years will add further information to our knowledge about the magnitude of screening benefit in different countries.

It has already convincingly been demonstrated that properly performed and interpreted mammography can detect breast cancer before it has grown to an incurable stage. The large-scale application of this capability can result in a substantial change of the breast cancer problem. By diagnosing most breast cancers in their early stages, therapeutic methods can be greatly influenced. Less mutilating therapy has a direct impact on the quality of life of the breast cancer patient. Additionally, mortality from this disease will be reduced significantly.

The study and control cohorts in Kopparberg county, Sweden, have been followed up for an average of 6.5 years since randomisation. This report described the results gained during this time in Kopparberg county on women aged 40–74 years at randomisation.

Proceedings of Symposium Mammographicum '85

Scientific Exhibition

Computer-assisted mammographic diagnosis, by A. G. Gale, K. Sole, E. J. Roebuck and B. S. Worthington
K-edge filters in mammography, by Y. Y. Y. Bakir, K. J. Plested, E. J. Roebuck, D. Whelpton and B. S. Worthington
Evaluation of mammographic film–screen systems, by Y. Y. Y. Bakir, D. Whelpton and B. S. Worthington
Magnetic resonance imaging of the breast using an experimental breast surface coil, by E. J. Roebuck, J. Tew, S. Chipperfield, P. Browning, J. Buckley and B. S. Worthington
Further results from the Marks & Spencer breast screening programme, by J. M. Haslehurst
Fact or artefact? by M. Yeowell and M. Mill
Muscular hamartoma of the breast, by B. J. Shepstone, C. A. Wells, A. R. Berry and J. D. P. Ferguson

COMPUTER-ASSISTED MAMMOGRAPHIC DIAGNOSIS

A. G. Gale, K. Sole, E. J. Roebuck and
B. S. Worthington

University Hospital, Nottingham

A reappraisal was made of the mammograms of 500 patients who had had both a mammogram and biopsy performed, specifically for the presence or absence of 43 mammographic signs. This information, together with histological data and the original radiological opinions, was subjected to stepwise discriminant analysis in order to identify the relative diagnostic importance of these signs both singly and in combination.

The database thus formed was subsequently used in conjunction with a locally designed computer program to predict the biopsy outcome (benign or malignant) in individual cases, based on the input of data relating to the presence or absence of those signs identified as being most significant. This resulted in a good separation of benign from malignant cases. A cross-validation test, using half the data base to analyse the signs present in the other half, also gave good separation of benign from malignant cases.

A comparison was then made between the computer prediction in each case and the original radiological opinion. The computer and radiologist were virtually equally efficient in predicting malignancy correctly, but the computer proved to be more accurate in the prediction of benign disease.

The use of this predicting technique is currently being evaluated for use by individuals of varying degrees of experience.

K-EDGE FILTERS IN MAMMOGRAPHY

Y. Y. Y. Bakir, *K. J. Plested, †E. J. Roebuck,
†D. Whelpton and †B. S. Worthington

*Kuwait Institute of Cancer Research, Sabah Hospital, Kuwait, *Nottingham General Hospital and †Queens Medical Centre, Nottingham*

The choice of target-filter systems in mammography is a compromise. The ideal system would allow high contrast with low radiation dose for all types of tissue structure in all types of breast. The Wisconsin Random Phantom was used to investigate a selection of K-edge filters with both tungsten and molybdenum target tubes. Surface and depth doses were measured, and the image contrast was assessed by spatial frequency analysis.

Extremely low doses can be achieved with some filters, but with low image contrast. Palladium filters (25 μm with molybdenum or 30 μ with tungsten anode) appear to offer the best compromise for either target, allowing reasonable tube loading and good image contrast with dose reductions of up to 35% compared with the molybdenum target and filter system. If emphasis is placed on minimising the dose, then the tungsten anode with palladium filter is preferable. However, the improved image contrast of the molybdenum anode with the palladium filter for all types of simulated lesion is likely to be more important than the factor of 1.4 increase in dose.

EVALUATION OF MAMMOGRAPHIC FILM–SCREEN SYSTEMS

Y. Y. Y. Bakir, *D. Whelpton and
*B. S. Worthington

*Kuwait Institute of Cancer Research, Sabah Hospital, Kuwait and *Queen's Medical Centre, Nottingham*

A variety of methods have been used to compare different radiographic systems. Ideally such methods should be objective, but should produce results which are compatible with those of subjective assessments.

Two different objective methods were compared to evaluate mammograms obtained using three different sets of parameters. Comparison between two systems, used to image the Wisconsin Random Phantom, was made using ROC analysis. This showed that all types of object in the phantom, simulated cancer masses, fibres and microcalcifications, were better imaged when using a molybdenum anode tube at 31 kVp, fitted with a 25 μm molybdenum filter, than with the other system, a tungsten anode tube, again filtered with 25 μm molybdenum, and operated at 28 kVp.

An alternative analysis was attempted using Fourier transforms to obtain the spatial frequency distribution corresponding to a single line of a microdensitometer scan of the image through the object being considered. This technique did not allow sufficiently accurate positioning of the microdensitometer light source on the film for microcalcifications to be investigated, but the method has been used for fibres and cancer masses. The parameter used to compare responses with the total area under the spatial frequency spectrum between the limits normally associated with human perception. The analysis showed that the response for the molybdenum anode system at 25 kVp was better than at 31 kVp, and that both systems were better than the tungsten anode arrangement.

In order to compare the findings with subjective assessments, a crude analysis of the object was made. This showed best response for the molybdenum system at 25 kVp, but was unable to separate the other two systems.

MAGNETIC RESONANCE IMAGING OF THE BREAST USING AN EXPERIMENTAL BREAST SURFACE COIL

E. J. Roebuck, J. Tew, S. Chipperfield, P. Brownrigg, J. Buckley and B. S. Worthington

University Hospital, Nottingham

Magnetic resonance imaging provides a method of imaging the breast without the use of ionising radiation. The criteria for differentiating benign from malignant lesions are similar to mammography: whether the outline of any mass is smooth or irregular, retraction of skin, involvement of intramammary and axillary lymph nodes and invasion of skin or muscle. Microcalcification cannot be assessed by MRI. The pectoral musculature is seen well. Transverse, sagittal, coronal and oblique views can be obtained. Multiple slice facility enables examination of the whole breast. Examples of MRI images correlated with the appropriate mammograms were shown for normal breast, mammary duct dysplasia and breast carcinoma. The images were obtained on a Picker International 0.15 T resistive machine using a breast surface coil.

FURTHER RESULTS FROM THE MARKS & SPENCER BREAST SCREENING PROGRAMME

J. M. Haslehurst

Marks & Spencer plc, London W1

Following a pilot study in 1972, Marks & Spencer offered breast screening on a regular basis to their staff in 1976. Screening is done every 15 months and includes personal and family history, clinical examination by a specialist nurse and mammography. Cranio-caudal and lateral oblique views are carried out routinely at the first visit, followed by lateral oblique films only at the second visit, unless there is a clinical indication for further films to be taken.

Since 1976, 30017 women have taken part in screening and the overall acceptance rate to the end of June 1985 is 84%. One hundred and ninety cancers were diagnosed by screening and 127 of these were under 2 cm in diameter. Of the 79 prevalence tumours, 57 were smaller than 2 cm and of the 111 incidence cancers, 70 were smaller than 2 cm though 23 of this group were of unknown size.

When node status has been assessed, over 80% of the cancers are node negative at diagnosis. In addition to the 190 screen-detected tumours, over 12 cancers were missed radiologically. Interval cancers are defined as a cancer developing after a truly negative screen and there were 49 of these in the period February 1976 to June 1985.

The 5-year survival has been assessed for a total of 68 cases. Of women under 50 years old, 93% have survived 5 years or longer and 85% of women over 50 years old have survived. It is too early yet to estimate 5-year survival of the interval cancers as numbers are too small. Seven out of 44 women with an interval cancer have died and their mean survival time is 27.5 months with a range of 2–26 months. Sixteen out of the 190 women with screen-detected cancers have a mean survival of 38.3 months with a range of 14–114 months. In both groups survival appears to compare favourably with non-screen-detected cancers.

FACT OR ARTEFACT?

M. Yeowell and M. Mill

BUPA Medical Centre, London WC1

Eight radiographic films were shown to demonstrate how artefacts can simulate pathology.

Film 1. Two lesions were seen: the lesion in the upper outer quadrant was benign; the apparent lesion in the lower quadrant was an artefact caused by the nipple shadow of the opposite breast.

Film 2. White patchy marks obscured breast detail—artefacts caused by a wet sponge pad.

Film 3. Scratch marks simulated macrocalcification.

Film 4. The microcalcification in the upper outer quadrant proved to be malignant. A finger print was also shown in the same area.

Film 5. Small scratch marks simulated fine microcalcification.

Film 6. Black spots obscured breast detail due to dried developer on the squeegee rollers of the processor.

Film 7. A foreign body behind the nipple was due to an impacted glass fragment.

Film 8. The scarring demonstrated was due to trauma. This patient had been bitten by a horse.

MUSCULAR HAMARTOMA OF THE BREAST

B. J. Shepstone, C. A. Wells, A. R. Berry and J. D. P. Ferguson

Oxford University and John Radcliffe Hospital, Oxford

This exhibit described the mammographic and histological appearances of a rare muscular hamartoma of the breast. The patient was a 52-year-old woman complaining of enlargement of the right breast. Mammography showed an oval, well demarcated, cystic-looking lesion about 8 cm in diameter, which was largely water-dense, but showed some central fat-dense areas. It was echogenic on ultrasonoscopy. Routine haematoxylin and eosin-stained sections of the excised specimen showed an outer layer of hyaline fibrous tissue, underneath which were expanses of loose collagen. Focal cellularity within this collagenous area was dominated by an elongated strap-like cell with the staining characteristics of smooth muscle. There was no nuclear pleomorphism or evidence of mitotic figures. Electron microscopy showed numerous smooth-muscle cells with myofilaments and surface pinocytic vesicles set within loose collagen. The smooth muscle is said to be derived from the walls of blood vessels, undifferentiated mesenchyme and myoepithelium (Davies, 1972; Davies & Ridell, 1973). Recovery was uneventful and recurrence is not expected. The case is described in greater detail elsewhere (Shepstone et al, 1985).

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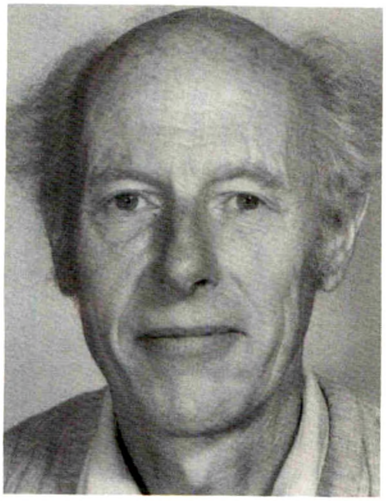
The 1986 BIR Awards winners

Dr David Kevin Bewley (Barclay Medal)



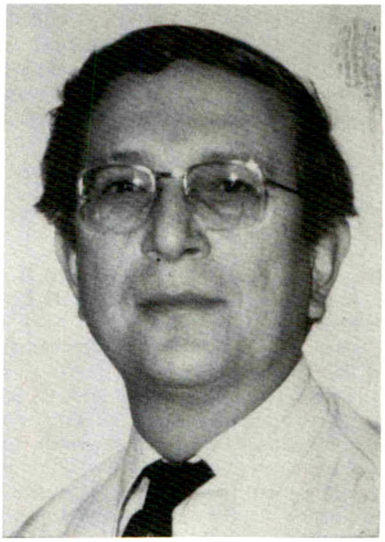
David Bewley graduated in physics from Cambridge in 1947, after three years spent at the Radar Research Laboratory in Malvern. He joined the physics staff at Hammersmith Hospital and became involved in bringing the 8 MeV linear accelerator into clinical use, including measuring its relative biological effectiveness (RBE) and developing its use for both total-body irradiation in early studies of kidney transplantation and electron treatments of mycosis fungoides. He developed a special interest in integral dose and began a series of studies on phantoms (starting with models of pregnant women impregnated with BD-2 ionisation chambers to measure fetal dose in diagnosis) and is still frequently seen wheeling various phantom bodies from one place to another for various purposes.

In 1957 Dr Bewley transferred to the MRC, continuing to work on both physical and radiobiological aspects of high-energy photons and subsequently neutrons and charged particles from the cyclotron. He made absolute dose measurements using calorimetry techniques, in the course of which he discovered the influence of dissolved oxygen on the "heat defect" in tissue-equivalent plastic. He was a key member of the team using pig skin to study neutron RBE and has been a guiding influence in the development of neutron therapy, including the three British programmes at Hammersmith, Edinburgh and Clatterbridge. More recently, he developed the current Hammersmith study of body composition using various nuclear methods (more phantoms).

Dr Bewley obtained his Ph.D. in 1961 and a D.Sc. in 1982. He has been Head of the Cyclotron Unit's Physics Department since 1962 and the Unit's Assistant Director since 1975. He has served on many committees including those of ICRU and ICRP and was the non-medical Editor of the *British Journal of Radiology* between 1975 and 1981. He won the Röntgen Prize in 1968. David Bewley has devoted his career to the study of physics relevant to medicine. His approach has always been a pragmatic one on a strong theoretical base. He was never known to shirk a tiresome job if he felt it worthwhile. David Bewley is a most deserving recipient of this year's Barclay medal.

S. B. Field

Professor Norman M. Bleehen (Röntgen Prize)

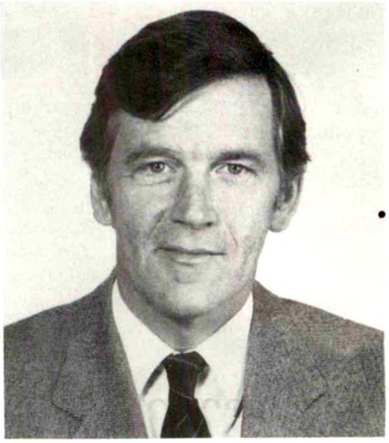


Norman Bleehen graduated from Exeter College, Oxford and did his clinical training at the Middlesex Hospital Medical School, qualifying in 1955. After registrar and senior registrar posts in the Radiotherapy Department at the Middlesex Hospital, he spent a year as a research fellow in the Department of Radiology at Stanford and, in 1969, was appointed Professor of Radiotherapy at the Middlesex Hospital. In 1975 he moved to Cambridge as Cancer Research Campaign Professor and Head of the University Department of Clinical Oncology and Radiotherapeutics and Director of the MRC Unit of Clinical Oncology and Radiotherapeutics. There he has built up a multidisciplinary team working on radiosensitisers, hyperthermia and other multimodality treatments of cancer. In 1984 he also became Director of the Radiotherapeutic Centre at Addenbrooke's Hospital, Cambridge.

Professor Bleehen has been actively involved in multicentre clinical trials: the MRC Cancer Trials Office in Cambridge is part of his Unit, and from 1969 to 1979 he was a member of the BIR Fractionation Working Party running the trial of three fractions per week versus five fractions per week in laryngo-pharyngeal cancer. He is chairman of the MRC Cancer Therapy Committee and the MRC Lung Cancer and Glioma Working Parties. His international reputation was recognised in 1984 when he was made an honorary fellow of the American College of Radiology. In 1985 he became President of the International Society for Radiation Oncology and he is a member of the EORTC Council. Amongst all his other numerous activities and commitments, we are pleased to record that he was a member of the BIR Council from 1974 to 1977.

J. L. Haybittle

Professor Michael Norman Maisey (Barclay Prize)



Professor Maisey was educated at Caterham School. After completing his medical training at Guy's Hospital Medical School, he joined the staff of Guy's Hospital, holding successively a number of posts in which his specialist interest in endocrinology began to develop.

In 1970 he was appointed Research Fellow at Johns Hopkins, obtaining the Diploma of the American Board for Nuclear Medicine in 1972. He then returned to Guy's, and, after a short spell as Senior Registrar, was appointed Consultant Physician in Endocrinology and Nuclear Medicine in 1973. In 1984 he was appointed to the newly-created Philip Harris Chair in Radiological Sciences, of the United Medical and Dental Schools of Guy's and St Thomas' hospitals, where he is currently involved in directing research into the clinical applications of nuclear magnetic resonance.

Professor Maisey is the author of many publications in the field of endocrinology and nuclear medicine, including a text book which has become a standard for radiologists training in nuclear medicine. His special interests range from thyroid disorders to myocardial imaging. He is a member of the Intercollegiate Committee for Nuclear Medicine and was appointed Honorary Consultant to the Army in Endocrinology and Nuclear Medicine in 1978.

Professor Maisey is married with two sons, and his hobbies include sailing and jazz appreciation.

N. W. Garvie

Obituary

Dr Benjamin Jolles, M.D., F.R.C.R., F.I.Biol., D.M.R.E., D.M.R.

Dr Benjamin Jolles died on November 7, 1985 in his 79th year.

His early history was not such as to suggest that he would become an integral part of British radiotherapy. He was born on November 26, 1906 in Lwow, then part of the Austro-Hungarian empire, but part of Poland after 1918. In 1925 his mother died of cancer and he formed the wish to become a cancer specialist; in the next year he went to study medicine in Florence and never returned to his native land. He qualified as an M.D. in 1931, having maintained himself largely by scholarships. In 1934 he translated a standard German textbook of radiology into Italian and a year later joined the staff of the radiology department in Florence. In 1938 he moved temporarily to Paris where, at the Institute Curie, he worked with Drs Lacassagne and Baclesse, and then to Britain, as a stateless person under the auspices of the Society for Protection of Science and Learning.

In 1939 he was awarded the first Duchess of Bedford Research Fellowship in Radiology, tenable at the Middlesex Hospital under Professor Russ. This was followed by two further years of training and experience in Manchester and Southampton, during which time he gained the D.M.R. In January 1944 Dr Jolles took up the appointment of Consultant Radiotherapist at Northampton General Hospital.

Over the next 28 years, until his retirement in 1972, Ben pursued his many research interests while striving always to improve the standard of service in his department. The number of patients attending the centre slowly increased to almost 1000 per year. In 1962, a purpose-built service and research radiotherapy department was opened. During the greater part of his time in Northampton, Dr Jolles worked single-handed and it remained his proud boast that his largest waiting list was one patient. His first concern was for the needs of the whole patient and he never allowed his many clinically orientated research interests to intrude into the management of individual patients. As a result he became very much a part of the scene of the City and County of Northampton and its hospitals.

Dr Jolles' research interests, which began in Italy and continued throughout his working life, covered a wide range of aspects of physics and biology all with a direct relevance to the care of patients. He is perhaps best known for propounding the theory and practice of "sieve X-ray therapy" based on the twin facts that relatively small areas or volumes of normal tissue will tolerate and recover from significantly higher doses of radiation than larger volumes and that this recovery is assisted by factors which enter the irradiated volume from adjacent unirradiated tissues. The application of his theories allowed larger doses of radiation to be delivered to underlying malignant tumours. In addition, he investigated changes in the vascular permeability of tumours during their development and treatment, the influence of connective tissue and stromal factors in the development of malignant disease and their influence on the outcome of treatment and the use of hormones in the management of patients with cancer. For example, he advocated the use of progestogens in ovarian cancer in 1962, an early paper in this field. Throughout his research work he recognised that the modification of existing modalities of treatment of patients with cancer, though important, was unlikely to lead to great or rapid improvements in results and felt that if a "breakthrough in treatment" were to come, it would probably be from an apparently unconnected field of study.

In his research work, Dr Jolles was closely associated with the British Empire Cancer Campaign and published many papers in important medical and scientific journals both in Britain and abroad, including a series of articles in the *British Journal of Radiology* between 1944 and 1970. He was a member of the British Institute of Radiology from 1944 to his death and also a member of the Faculty of Radiologists from 1942 and was elected Fellow without Examination in 1970. In addition, the Institute of Biology recognised his research activities by making him a fellow.

Ben supported very many radiological meetings in Britain during his long active career and frequently posed pertinent and piercing questions, nor would he be put off easily by a superficial or inadequate answer.

After Dr Jolles retired in 1972, he continued to demonstrate a long-term and sincere concern for patients. Largely as a result of his efforts, Northampton now has the Cynthia Spencer House, which was opened as a continuing care unit by Her Majesty The Queen Mother in 1976, and an extension to that unit, for additional day care of patients with advanced cancer, opened by Her Royal Highness The Princess of Wales.

In 1947 he took British nationality, and in the same year married Miriam, who survives him with their three children.

W. M. Ross

Retirement of Douglas Currie

Mr Douglas Currie, who for 22 years has been the mainstay of the BIR as house manager and caterer, will retire with Mrs Currie to Haddington, East Lothian, in August 1986. Douglas and Betty Currie have not only taken good care of Welbeck Street and Portland Place, but also cared for the members and staff in a way that assures them of a special place in the history of the Institute and in the hearts of all connected with it.

A buffet lunch will be given to honour Mr and Mrs Currie at 1 pm on July 23 1986 in the Library at 36 Portland Place. A contribution of £5 per head is requested from those able to attend. In addition, a presentation will be made to Mr and Mrs Currie on behalf of members, and contributions are invited.

Please write to the General Secretary to say whether you will be able to come, enclosing a cheque payable to the BIR.

Whatever happened to 32 Welbeck Street?

Members will be interested to know that the Variety Club of Great Britain, who now occupy our old home, 32 Welbeck St, have decided to restore the lecture theatre to its former beauty as a Russian Church. It was built in 1860 as the church of the Russian embassy, and the restoration work includes murals with the main theme of healing the sick, and roundels in the dome depicting the twelve apostles. These are being painted by Helen Grunwald, who has previously painted a large mural at St Thomas' Church, Canterbury. When work is completed, the church will be open to the public.

Picture courtesy of Mr Kin Lee.

Radiation warning signs

The Editor–Sir,

I was interested to read in the January *Bulletin*, an article by D. Gifford on radiation warning signs. The following comments may be helpful in respect of labelling controlled areas.

From discussions with the Health and Safety Executive, both locally and nationally, the very strong recommendation being made is that controlled areas around fixed radiation generators should not be designated temporarily. Thus, radiation warning signs should be permanently placed where there is a potential hazard. Removing and replacing signs will only serve to confuse staff and patients and may even lead to accidents. Access to the controlled areas when equipment is not being used can easily be detailed in the local rules.

Schemes of work which are required for controlled areas can be quite simple affairs and should cause no alarm. For example, a system of work to cover cleaners entering after normal working hours (when the X-ray room may still be in use) could simply be:

(a) warning lights and notices at the entrance to X-ray rooms must be observed, and

(b) persons who are not trained in the use of X-ray equipment must be supervised by a member of the radiographic staff, unless they have ascertained that the equipment is switched off at the control unit.

Indeed, these instructions were probably being followed before the Regulations came into existence and there is consequently no need to have removable controlled area notices on the doors to the X-ray room.

Yours, etc.

Dr P. J. Roberts

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Queen Elizabeth Medical Centre,
Birmingham B15 2TH

Press Releases

Health physics research abstracts

The International Atomic Energy Agency's publication *Health Physics Research Abstracts: Information on Research in Progress* (the HPRA bulletin) contains preliminary information useful to investigators studying problems in health physics. The HPRA bulletin provides possibilities for researchers to obtain further information and advice from other scientists in their field. It thereby helps to avoid duplication of work and to reduce costs. The publication is also intended to assist developing Member States in finding proper expertise for conducting their own research programmes.

The Secretariat of the Agency would very much appreciate receiving abstracts on research in progress, prepared in accordance with instructions which are available through Paul Ashton, Health Services Division, DHSS, Hannibal House, Elephant and Castle, London SE1 6TE (Tel. 01-703 6380).

Arab Health

Arab Health is a bimonthly journal dealing with topics in the health care industry, covering the latest developments in health care management, medical technology and the pharmaceutical industry. It is published in a bilingual Arabic-English format and is strictly tailored to serve all those involved in the purchase of medical equipment and supplies in the Middle East and Africa.

For a sample copy of *Arab Health* and the 1986 media file, please contact: The Service Department, *Arab Health,* PO Box 13-5300, Beirut, Lebanon.

New cobalt unit from AECL

The new Phoenix Cobalt Therapy Unit is a simplified version of the Theratron series of units. The Phoenix features 200 Rmm head capacity, manual collimator with 35 cm clearance between isocentre and collimator, local control suspended from an overhead support arm, an interlock system with information displayed on the timer panel to indicate conditions that stop or prevent treatment, and manual control of all motions except gantry rotation and table vertical.

The Theratron 780C is AECL Medical's most advanced cobalt unit. It is fully motorised, capable of meeting the most stringent regulations, and upgradeable to fit any computerised clinic.

Research opportunities in North America

The National Medical Researcher Matching Program (NMRMP) is an information service that attempts to match professional opportunities in post-doctoral medical research, in the United States and Canada, with eligible individuals worldwide. These individuals can be M.D.s and Ph.D.s or equivalent, foreign degree holders in medical or health related areas, who are interested in conducting research in the United States or Canada.

By operating a computerised information network which maintains direct contact with over 80 000 medical research directors in the United States and Canada, the NMRMP is able to provide the eligible individuals with information regarding at least 10 research opportunities four times a year, according to the individual's preferred specialisation.

For detailed information, prospective applicants may contact: National Medical Researcher Matching Program, 1109 Main Street, Suite C, Boise, Idaho 83702 USA (Tel: 208-336 7387, 336 7397).

Laboratory Animal Science Association

The object of the above Association is: to promote the advancement of laboratory animal science for the benefit of the public; to promote the interchange of scientific information among persons interested in laboratory animal science by means of meetings, lectures, demonstrations, discussions and publications as appropriate; to encourage education and training in laboratory animal science; to co-operate with other bodies interested in laboratory animal science, welfare and technology.

Two general meetings are held each year. These usually consist of a symposium held in May, and a meeting in November at which members can submit communications. Study groups on various topics (including pathology, infectious diseases, laboratory techniques) also hold individual specialist meetings throughout the year.

The official journal of the Association is called *Laboratory Animals* and copies are supplied free to members. From time to time specialist "Laboratory Animal Handbooks" are produced on topics of particular interest.

Further information from: Dr B. Waynforth, Animal Unit, The Charing Cross and Westminster Medical School, St Dunstan's Road, London W6 8RP (Tel. 01-748 2906).

Automatic biopsy device now available in UK

In 1982 Radiplast AB, working in conjunction with radiologists at Uppsala Hospital, Sweden, produced a device designed to improve the technique of obtaining specimens using the well established needle cut principle.

The "Biopty", which is now available in the UK, makes it possible to perform the biopsy procedure with one hand, leaving the other hand free to manoeuvre the ultrasound transducer or immobilise the lesion.

The actual operation of the Biopty is quicker and easier to perform than to describe. The instrument is spring loaded by pulling back the handle, and the needle is placed in position. The Biopty is then held in one hand and, when ready, the trigger is depressed. The obturator is fired and when it reaches the limit of its travel it automatically triggers a system which immediately advances the cannula over the obturator, cutting off the prolapsed tissue in the notch of the obturator. The two different movements of the cannula and obturator are automatic and precise and, as a result, excellent specimens suitable for histology as well as cytology are obtained. The Biopty is made of aluminium and stainless steel and can be autoclaved. At present there are two sizes of Biopty-Cut needles available; an 18 gauge with a sampling notch length of 17 mm and a 14 gauge with a sampling notch length of 20 mm.

For further information contact: X-Ray Division, Henleys Medical Supplies Ltd, London N8 0DL (Tel. 01-889 3151).

Library news

The BIR Library is open weekdays 9am–5pm

The Librarian, Mrs Gunnel Ingham, is in attendance Tuesdays 11am–4pm, and Thursdays 11am–7pm. Mrs Angela Lansdown, daily 9am–5pm.

The journal stock includes more than 100 titles. Though journals may not be taken out of the library, there is a photocopy service, also available by post. A list of current journals is available on request and is also published in the Bulletin twice a year.

Most books (excepting the historical collection) are available on loan.

Further information: telephone 01-580 4085.

Recent additions to the Library

Caffey's Pediatric X-ray diagnosis. 8th edit. by F. N. Silverman. Vol. 1–2. 1985

Deconinck, F. (Ed.): Information processing in medical imaging. 1984

Freedom, R. M., Culham, J. A. G. & Moes, C. A. F.: Angiocardiography of congenital heart disease. 1984

HMSO: Ionising radiation regulations. 1985

NCRP Report No. 82: SI units in radiation protection and measurements. 1985

Stoll, B. A. (Ed.): Cancer treatments. End-point evaluation. 1983

WHO: Nuclear power: health implications of transuranium elements. 1982

New journal: Current opinion in cardiology

BIR Calendar Events

Unless otherwise indicated, enquiries about the following events should be addressed to the Assistant Secretary: Programme, British Institute of Radiology, 36 Portland Place, London W1N 3DG (Tel. 01-580 4085).

The meetings are at 36 Portland Place unless otherwise stated.

Attendance is open to non-members

Conversazione

June 19, 1986 at 6.30 pm

Royal Society of Medicine, London W1

Incorporating the Silvanus Thompson Memorial Lecture: "Seeing through illusion", by Professor R. L. Gregory.

Joint RCR/BIR/RSM Autumn Provincial Meeting; RCR Annual General Meeting

September 11–13, 1986

University of Sheffield

Organised by the RCR. Further details from the Meetings Secretary, The Royal College of Radiologists, 38 Portland Place, London W1N 3PG (Tel. 01-636 4432/3).

Advance Notice

British Institute of Radiology 45th Annual Congress

incorporating the joint BIR/RCR/RSM (Section of Radiology) spring meeting

RADIOLOGY '87

University of Southampton

April 1–3, 1987

The Congress will cover all aspects of radiology—X-ray diagnosis, radiotherapy, radiation oncology, nuclear medicine, ultrasound, NMR, radiological physics, radiobiology, radiation protection and related disciplines and is expected to include:

The Mackenzie Davidson Memorial Lecture

The Mayneord Lecture (BIR)

The George Simon Lecture (RCR)

The BIR Presidential Address

Major technical exhibition

Scientific exhibition

Proffered papers are invited. Please apply for form from the BIR. Absolute closing date for receipt of completed proffered paper forms is November 30, 1986.

For further information please apply to the Assistant Secretary: Programme, The British Institute of Radiology, 36 Portland Place, London W1N 3DG (Tel. 01-580-4085).

Picker introduces Vista 2055HP MRI

Picker International has added to its range of magnetic resonance scanners with the high performance Vista 2055HP. The new system is designed specifically for clinical imaging and spectroscopic research. A choice of superconductive magnets at field strengths up to 2 T provides the maximum flexibility in imaging at 0.5 T, 1.0 T and 1.5 T, and spectroscopic research at 1.5 T and 2.0 T.

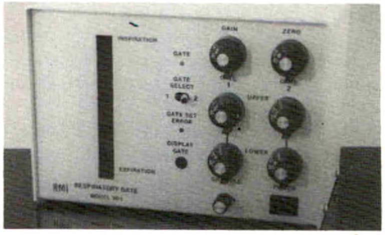
The system offers a variety of post-processing display and analysis features, including a 512 × 512 acquisition and display matrix, and powerful multitasking software. It also enables contiguous multislice, multiecho imaging and offers 3D Fourier transform volume scanning techniques for multinuclear and ultrathin slice scanning. True direct oblique images are obtainable with the 2055HP, as is imaging in axial, sagittal and coronal positions.

For body scanning, motion artefacts have been significantly reduced by COPE™ software, with virtually no change in scan time. Fast scanning is available to the VISTA 2055HP user, with the Hybrid™ fast scan technique enabling 2D and 3D Fourier transform data acquisition up to four times faster than the normal rate.

For further information, please contact: Iain MacRae, Marketing Service Manager, Picker International Ltd, PO Box 2, East Lane, Wembley, Middx HA9 7PR (Tel. 01-904 1288).

Respiratory gating system

Radiation Measurements, Inc. introduces a respiratory gating system, Model 301, which monitors patient respiration with each individual breath. No "averaging" is needed. This system provides good images, regardless of changes or irregularities in the patient's respiration during imaging. The gate signal is a TTL signal transferred via a BNC connector. The gating system has been tested on a 0.5 T superconducting MR system.



Meetings, Courses, Notices

As a service to our readers, the title, date and place of meetings and contact address will be inserted free of charge: any additional information will be charged at £1.75 per printed line, per insertion. Please contact the Managing Editor.

Computers for the Practising Physician: Update 1986

July 27–30, 1986, New Seabury, Cape Cod, Massachusetts
Further Details: Department of CME, Boston University School of Medicine, 80 East Concord Street, Boston, MA 02118, USA.

International Conference on Theories of Carcinogenesis. Facts, fashion or fiction?

August 16–20, 1986
Oslo, Norway
Further details: University of Oslo Congress Service, PO Box 55—Blindern, N-0313 Oslo 3, Norway.

4th International Congress on Interventional Ultrasound.

August 19–22, 1986
Copenhagen, Denmark
Further details: Spadille Congress Service, DK-3100 Hornbaek, Denmark.

International Symposium on Radiotherapy in Developing Countries

September 1–5, 1986
Vienna, Austria
Further details: Y. Skoropad, IAEA, Division of Life Sciences, PO Box 100, A-1400 Vienna, Austria.

Paediatric Radiology Course

September 8–10, 1986
Sheffield
Basic paediatric imaging for consultants and senior registrars to enable them to face problems in the DGH and FRCR.
Further details: Dr G. M. Steiner, X-ray Department, Sheffield Childrens Hospital, Western Bank, Sheffield S10 2TH (Tel. 0742-71111).

International Symposium on Transrectal Ultrasound in the Diagnosis and Management of Prostate Cancer

September 11–12, 1986
Renaissance Center, Detroit, Michigan, USA
Further details: Mr Jerry Dowty, Dept of Radiology, Catherine McAuley Health Center, PO Box 995, Ann Arbor, Michigan 48106, USA (Tel. 313-572 5251).

Giornate Italo Francofone di Radiologia Pediatrica

September 12–13, 1986
Capri, Italy
Further details: Organising Secretariat, IDELSON Congressi, Via A. de Gasperi 55, 80133 Napoli, Italy (Tel. 081-320741).

4th European Congress and 13th Regional Congress of the International Radiation Protection Association

September 15–19, 1986
Salzburg, Austria
Further details: Congress Secretary, Österreichisches Forschungszentrum Seibersdorf, A-2444 Seibersdorf, Austria.

3rd Congress of the European Society for Magnetic Resonance in Medicine and Biology

September 21–24, 1986
Aberdeen
Further details: Organising Secretary, Dr M. A. Foster, Department of Biomedical Physics, University of Aberdeen, Foresterhill, Aberdeen.

7th Annual Study Day: The Role of the Plain Abdominal X ray in the Acute Abdomen

September 24, 1986
Kent Postgraduate Medical Centre, Canterbury
Further details: Postgraduate Administrator, Kent Postgraduate Medical Centre, Kent and Canterbury Hospital, Canterbury, Kent CT1 3NG (Tel. 0227-66877 ext. 4367).

Basic Review and Current Concepts in Neuroradiology and Head and Neck Radiology

A Harvard Medical School Postgraduate Course
September 29–October 3, 1986
Boston Marriott Hotel, Boston
Further details: Harvard Medical School, Dept of CME, Boston MA 02115, USA (Tel. 617-732 1525).

Radiology Update

November 7–8, 1986
Cape Town, South Africa
Further details: Prof. B. J. Cremin or Mrs Elliot, Postgraduate Medical Centre, UCT Medical School, Observatory 7925, Cape Town, South Africa (Tel. 021-47 1250).

3rd European Symposium on Radiopharmacy and Radiopharmaceuticals

May 1–4, 1987
Elsinore, Denmark
Further details: Elisabeth Nørbygaard, The Isotope Pharmacy, 378 Frederikssundsvej, DK-2700 Brønshøj, Denmark.

Conference on Health Effects of Low Dose Ionising Radiation—Recent Advances and Their Implications

May 11–14, 1987
Royal Institute of British Architects, London
Further details: The Secretariat, British Nuclear Energy Society at the Institution of Civil Engineers, 1–7 Great George Street, London SW1P 3AA (Tel. 01-630 0726).

VI Congress of the European Association of Radiology (ECR '87)

May 31–June 6, 1987
Lisbon, Portugal
Further details: Secretariat ECR '87, SPRMN, Av. Elias Garcia, 123–7° DTo, 1000 Lisboa, Portugal, (Tel: 77–05 30; Telex 62074 SPRMN P).

Ninth International Conference on the Use of Computers in Radiation Therapy

June 22–25, 1987
The Hague
Further details: Organisation IX ICCR, Ir. P. H. van der Giessen, Dr. Bernard Verbeeten Institute, P.O. Box 90120, 5000 LA Tilburg, The Netherlands, (Tel. 013 655 725).

4th International Symposium on Audiological Medicine

November 8–11, 1987
Tenerife, Canary Islands
Further details: Dr Jose Barajas, Perez de Rozas 8, 38004 Santa Cruz de Tenerife, Spain.

THE BRITISH INSTITUTE OF RADIOLOGY

PUBLICATIONS

☐ **Basic Clinical Ultrasound** Hylton B. Meire and Pat Farrant (British Institute of Radiology Teaching Series No. 4)	1982	£12.00
BIR Supplements:		
☐ 16. **Treatment Simulators (Applications of Modern Technology in Radiotherapy)**	Revised 1981	£3.50
☐ 17. **Central Axis Depth Dose Data for Use in Radiotherapy** This standard work replaces BJR Supplement 11 (1972)	1983	£8.00
☐ 18. **Quality Assurance** Proceedings of a CEC/CRAD scientific symposium on criteria and methods for quality assurance in medical X-ray diagnosis, Udine (Italy), April 1984	1984	£16.00
☐ BJR Reprints **Fractionation Study: Radiotherapy of the laryngopharynx** (*BJR*, 1982, *55*, 505–510) Seventh interim progress report		75p
☐ **Review Article: The Radiological Effects of Nuclear War** (*BJR*, 1983, *56*, 147–170) Report of a BIR Working Party		£1.95
☐ **Review Article: Biomedical Applications of the Relaxation Behaviour of Water Related to NMR Imaging** (*BJR*, 1984, *57*, 955–976) R. Mathur de Vré		£2.00

To: Publications Department
The British Institute of Radiology
36 Portland Place
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The British Institute of Radiology Nycomed Scandinavian Scholarships 1987

The British Institute of Radiology invites applications for the 1987 Nycomed Scandinavian Scholarships.

These Scholarships, which are generously funded by Nycomed (UK) Ltd, enable United Kingdom diagnostic radiologists, preferably members of the British Institute of Radiology, to visit Scandinavian academic departments for up to two months' concentrated study, free of financial constraints: a maximum of £2500 per month will be provided.

The purpose of the Nycomed Scandinavian Scholarships is to enable diagnostic radiologists of senior registrar or junior consultant status, interested in diagnostic or interventional procedures concerned with intravascular contrast media, to visit one or more academic departments of radiology in Scandinavia (Norway, Sweden, Denmark) for in-depth radiological experience of up to two months. Each recipient will be responsible for his/her itinerary, travel, accommodation and insurance arrangements, subject to the approval of the BIR.

A condition of each scholarship is that a report of work undertaken, in a form suitable for publication in the Bulletin of the British Institute of Radiology, shall be submitted.

Applications for 1987 should be submitted by the end of July 1986 and interviews will take place in September.

Nyegaard (UK) Limited wishes to announce there has been a change of Company name to : NYCOMED (UK) LIMITED.

For further information please write to:
The General Secretary
The British Institute of Radiology
36 Portland Place
London W1N 3DG

(continued from outside back cover)

Book reviews

	Page
Radiology of adverse reactions to drugs and toxic hazards. *G. Ansell*	596
Carbon-14 in the environment. NCRP Report No. 81	596
Radionuclide imaging techniques. *P. F. Sharp, P. P. Dendy and W. I. Keyes*	608
Nuclear imaging in pediatrics. *A. R. Siddiqui*	622
BIR Bulletin and calendar events	*facing page* 642

British Journal of Radiology Supplement 19

Radiation Damage to Skin

Fundamentals and Practical Aspects

Proceedings of a Workshop held at Saclay, France, on October 9–11, 1985, organised by the Commission of the European Communities and the Commissariat à l'Energie Atomique de Protection et de Sûreté Nucléaire, Fontenay-aux-Roses, France.

Skin and underlying tissues are frequently critical structures in radiological protection. Over exposure to ionising radiation can cause serious long-term suffering and disability.

Despite their practical importance, the dose-effect relationships, the pathophysiological mechanisms and the influence of the degree to which different tissues are involved are still poorly understood.

This Workshop and Proceedings bring together those at the forefront of research in these areas from all over the world. They review the present state of knowledge and attempt to identify specific problem areas which may lead to recommendations for the improvement of radiological protection and for the better management of radiation accidents.

Radiation Damage to Skin is, therefore, a vital reference work for everyone working in radiation protection and dosimetry.

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ISSN 0007-1285
Available June 1986

Price £18.00 including postage and packing
About 200 pp.; illustrated

Orders to: The Publications Department, The British Institute of Radiology, 36 Portland Place, London W1N 3DG. Tel: 01-580 4085.

VOL 59 NO 702 JUNE 1986

The British Journal of Radiology

Contents

Page

Reactions to radiographic contrast media: an attempt to detect specific anti-contrast medium antibodies in the sera of reactor patients 531
A. C. Walker and D. H. Carr

Tissue analysis by dual-energy computed tomography 537
D. J. Hawkes, D. F. Jackson and R. P. Parker

Prominent periportal echogenicity: its sonographic evaluation and its significance 543
E. M. T. Chau, L. L. Y. Leong and F. L. Chan

Sarcoidosis of the parotid gland 547
B. O. Iko, C. E. Chinwuba, E. M. Myers and J. S. Teal

Measurement of total lung water from nuclear magnetic resonance images 553
F. M. MacLennan, M. A. Foster, F. W. Smith and G. A. Crosher

Magnetic resonance imaging and hydatidiform mole 561
M. C. Powell, J. Buckley, B. S. Worthington and E. M. Symonds

A method for the clinical measurement of relaxation times in magnetic resonance imaging 565
D. S. Hickey, D. Checkley, R. M. Aspden, A. Naughton, J. P. R. Jenkins and I. Isherwood

Fast computer processing for tissue highlighting in computed tomographic cross-sectional imaging and digital scan projection radiography 577
C. J. Moore and B. Eddleston

Oedema of the neck after ablation of the thyroid with radioactive iodine 583
A. W. G. Goolden, K. C. Kam, M. L. Fitzpatrick and A. J. Munro

Late radiation response of kidney assayed by tubule-cell survival 587
H. R. Withers, K. A. Mason and H. D. Thames Jr

Protection against ionising radiation and synergism with thiols by zinc aspartate 597
G. L. Floersheim and P. Floersheim

Technical note

A technique for velocity imaging using magnetic resonance imaging 603
J. P. Ridgway and M. A. Smith

Case reports

Congenital pleural effusion in Down's syndrome 609
K. D. Foote and D. W. Vickers

Intravascular papillary endothelial hyperplasia of the adrenal gland 610
A. Kawashima, T. Johsen, S. Murayama and W. J. Russell

Technetium-99m Medronate uptake in subcutaneous soft-tissue nodules in a patient with renal failure and renal adenocarcinoma 613
J. C. Macmillan, S. J. Scott, M. I. McHugh and E. D. Williams

Menetrier's disease in childhood associated with cytomegalovirus injection: a case report and review of the literature 615
N. A. G. Coad and K. J. Shah

Fatal acute vasculitis after high-dose urography with iohexol 620
T. Goodfellow, G. E. Holdstock, F. J. Brunton and J. Bamforth

Case of the month

Diagnosis of a right iliac fossa mass by computed tomography 623
S. J. McLaughlin, J. G. Gray and M. Braithwaite

Short communication

Protection of mouse chromosomes against whole-body gamma irradiation by SH-compounds 625
R. Gupta and P. U. Devi

Correspondence

The tissue-rescuing unit 628
J. H. Hendry and H. D. Thames

Assessment of the current use of rare-earth screens in the United Kingdom 630
J. G. B. Russell

Proceedings of Symposium Mammographicum '85 631

(continued on inside back cover)

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